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(54) Title: METHODS FOR THE TREATMENT OR PREVENTION OF CONDITIONS ASSOCIATED WITH AMYLOIDOGENIC REPTIDES

(57) Abstract

This invention provides methods for the treatment or prevention of physiological disorders associated with an amy loidogenic peptide by the administration of a series of substituted naphthalenes, dihydronaphthalenes, benzofurans, benzothiophenes indoles, or the pharmaceutically acceptable salts or solvates thereof. This invention also provides methods for the treatment or prevention of Alzheimer's Disease or Down's Syndrome by the administration of these same benzofurans or benzothiophenes or the pharmaceutically acceptable salts thereof.

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METHODS FOR THE TREATMENT OR PREVENTION OF CONDITIONS ASSOCIATED WITH AMYLOIDOGENIC PEPTIDES

Alzheimer's disease is a degenerative disorder of the human brain. Clinically, it appears as a progressive dementia. Its histopathology is characterized by degeneration of neurons, gliosis, and the abnormal deposition of proteins in the brain. Proteinaceous deposits (called "amyloid") appear as neurofibrillary tangles, amyloid plaque cores, and amyloid of the congophilic angiopathy. [For a review, see, D.J. Selkoe, Neuron, 6:487-498 (1991)]

While there is no general agreement as to the chemical nature of neurofibrillary tangles, the major constituent of both the amyloid plaque cores and the amyloid of the congophilic angiopathy has been shown to be a 4500 Dalton protein originally termed β-protein or amyloid A4. Throughout this document this protein is referred to as β-amyloid peptide or protein.

β-amyloid peptide is proteolytically derived from a transmembrane protein, the amyloid precursor protein. Different splice forms of the amyloid precursor protein are encoded by a widely expressed gene. see, e.g., K. Beyreuther and B. Müller-Hill, Annual Reviews in Biochemistry, 58:287-307 (1989). β-amyloid peptide consists, in its longest forms, of 42 or 43 amino acid residues. J. Kang, et al., Nature (London), 325:733-736 (1987). These peptides, however, vary as to their amino-termini. C. Hilbich, et al., Journal of Molecular Biology, 218:149-163 (1991).

Because senile plaques are invariably surrounded by dystrophic neurites, it was proposed early that β-amyloid peptide is involved in the loss of neuronal cells that occurs in Alzheimer's disease. B. Yankner and co-workers were the first to demonstrate that synthetic β-amyloid peptide could be neurotoxic in vitro and in vivo. B.A. Yankner, et al., Science, 245:417 (1989); See, also, N.W. Kowall, et al., Proceedings of the National Academy of Sciences, U.S.A.,

88:7247 (1991). Other research groups, however, were unable to consistently demonstrate direct toxicity with β-amyloid peptide. See, e.g., Neurobiology of Aging, 13:535 (K. Kosik and P. Coleman, eds. 1992). Even groups receiving β-amyloid peptide from a common source demonstrate conflicting results. P. May, et al., Neurobiology of Aging, 13:605-607 (1992). Resolution of this controversy was achieved once a better understanding of the role of secondary conformation of β-amyloid peptide as it relates to neurotoxicity was achieved. Now, numerous researchers report direct neurotoxicity of β-amyloid peptide.

In addition to Alzheimer's disease, Down's syndrome is also characterized by an accumulation of β-amyloid peptide. In patients suffering from Down's syndrome the β-amyloid peptide is the primary constituent of senile plaques and cerebrovascular deposits.

Recently, it has been shown that β-amyloid peptide is released from neuronal cells grown in culture and is present in cerebrospinal fluid (CSF) of both normal individuals and those persons suffering from Alzheimer's Disease. See, D. Seubert, et al., Nature (London), 359:325-327 (1992).

A possible correlation to the plaque pathology has been developed by several groups demonstrating the direct β-amyloid peptide-induced neurotoxicity toward cultured neurons.

More recently, in addition to the direct neurotoxicity, an inflammatory response in the Alzheimer's Disease brain, perhaps elicited by β-amyloid peptide, also contributes to the pathology of the disease. A limited clinical trial with the non-steroidal anti-inflammatory drug indomethacin exhibited a retardation in the progression of Alzheimer's dementia. Rogers et al., Science, 260:1719-1720 (1993).

Direct neurotoxicity of β-amyloid peptide was recently reported to be attenuated by co-treatment with beta transforming growth factor (TGF-β). Chao et al., Society of

Neurosciences Abstracts, 19: 1251 (1993). The beta transforming growth factors are multifunctional cytokines produced by many types of cells, including hematopoietic, neural, heart, fibroblast, and tumor cells, that can regulate the growth and differentiation of cells from a variety of tissue origins. Sporn, et al., Science, 233:532 (1986). There are at least five isoforms of TGF-β currently identified.

TGF-β has been shown to have numerous regulatory actions on a wide variety of both normal and neoplastic cells. This protein is multifunctional, as it can either stimulate or inhibit cell proliferation, differentiation, and othr critical processes in cell function. For a general review of TGF-β and its actions, see Sporn, et al., Journal of Cell Biology, 105:1039-1045 (1987); Sporn and Roberts, Nature (London), 332:217-219 (1988); and Roberts, et al., Recent Progress in Hormone Research, 44:157-197 (1988).

In addition to Alzheimer's Disease and other conditions associated with the amyloidogenic peptide β-amyloid peptide, there exist conditions associated with other amyloidogenic peptides which are structurally similar to β-amyloid peptide but which share no sequence homology with the β-amyloid peptide. Recent studies have demonstrated the functional interchangeability of many of these amyloidogenic peptides with regard to neurotoxicity. P.C. May, et al., Journal of Neurochemistry, 61:2330-2333 (1993); co-pending U.S. Patent Application 08/109,782, filed August 19, 1993.

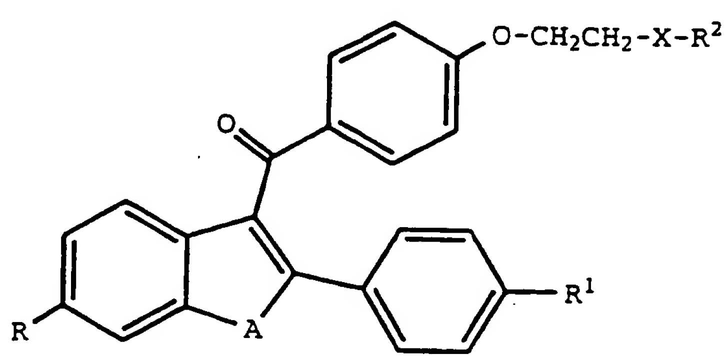
Human amylin (also known as diabetes-associated peptide and islet amyloid polypeptide) is a 37 amino acid peptide first isolated from amyloid deposits in the pancreas of non-insulin-dependent diabetic individuals. C.J.S. Cooper et al., Proceedings of the National Academy of Sciencs (USA), 84:8628-8632 (1987). The rat homologue of amylin is 95% similar in primary sequence to human amylin but has amino acid substitutions in the region conferring β-pleated

secondary structure which render it non-amyloidogenic. See, e.g., J. Asai et al., Biochemical and Biophysical Research Communications, 164:400-405 (1989); L.R. McLean and A. Balasubramaniam, Biochimica and Biophysica Acta, 112:317-320 (1992).

β_2-microglobulin is another protein unrelated to β-amyloid peptide but capable of forming amyloid deposits in the kidney. [for recent review, see, J.M. Campistol and M. Skinner, Seminars in Dialysis, 6:117-126 (1993)]. This nonpolymorphic peptide is homologous to the C3 domain of the immunoglobulin class IgG and is one subunit of class I major histocompatibility antigens.

Because of the debilitating effects of Alzheimer's disease, Down's syndrome, and these other conditions associated with amyloidogenic peptides and proteins there continues to exist a need for effective treatments. This invention provides compounds efficacious in the treatment and prevention of these disorders.

This invention encompasses a method for the inhibition of a physiological disorder associated with an amyloidogenic peptide, which method comprises administering to a mammal in need thereof an effective amount of a compound of Formula I



I

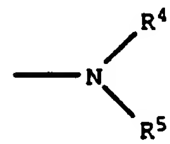
wherein:

A is -O-, $-S(O)_m-$, $-N(R^{11})-$, $-CH_2CH_2-$, or -CH=CH-;

m is 0, 1, or 2;

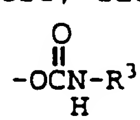
X is a bond or C_1-C_4 alkylidenyl;

R^2 is a group of the formula



wherein R^4 and R^5 are independently C_1-C_6 alkyl or combine to form, along with the nitrogen to which they are attached, a heterocyclic ring selected from the group consisting of hexamethyleneiminyl, piperazino, heptamethyleneiminyl, 4-methylpiperidinyl, imidazolinyl, piperidinyl, pyrrolidinyl, or morpholinyl;

R is hydroxy, halo, hydrogen, C_3-C_8 cycloalkyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkoxy, or phenyl, said phenyl being optionally substituted with one, two, or three moieties selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, chloro, fluoro, trifluoromethyl $-OSO_2-(C_1-C_{10}$ alkyl)

or  ;

R^1 is hydroxy, halo, hydrogen, C_3-C_8 cycloalkyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkoxy, or phenyl, said phenyl being optionally substituted with one, two, or three moieties selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro,

chloro, fluoro, trifluoromethyl $-OSO_2-(C_1-C_{10}$ alkyl) or $-OC(=O)N(H)-R^3$;

each R^3 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl where the substituent is halo, C_1-C_6 alkyl or C_1-C_6 alkoxy;

with the proviso that when X is a bond and A is -S-, R and R^1 are not both selected from the group consisting of hydroxy, methoxy, and C_2-C_7 alkanoyloxy;

or a pharmaceutically acceptable salt or solvate thereof.

The present invention also provides a method of inhibiting amyloidogenic peptide production comprising administering to a mammal in need thereof an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of increasing TGF-β expression in the brain, comprising administering to a human in need thereof an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof.

The present invention also provides a method of inhibiting the inflammatory response associated with Alzheimer's Disease comprising administering to a human in need thereof an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof.

The term "amyloidogenic peptide" refers to those peptides which have the ability to self-associate into higher ordered aggregates and eventually assemble into an amyloid

plaque. An especially preferred amyloidogenic peptide target in methods of this invention is the β-amyloid peptide.

As used herein the term "inhibit" or "inhibiting" includes its generally accepted meaning which encompasses prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or a resultant symptom. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

The term "physiological disorder associated with an amyloidogenic peptide" includes diseases related to the inappropriate or undesirable deposition, such as in the brain, liver, kidney, or other organ, of at least one amyloidogenic peptide, and as such includes Alzheimer's Disease (including familial Alzheimer's Disease), Down's Syndrome, advanced aging of the brain, hereditary cerebral hemorrhage with amyloidosis of the Dutch-type (HCHWA-D), and the like.

The term "effective amount" as used herein refers to the amount of compound necessary to inhibit physiological effects or disorders associated with an amyloidogenic peptide, or inhibit amyloidogenic production or deposition, or inhibit Alzheimer's Disease, as the case may be.

The term "conservative variant" as used herein refers to amino acid substitutions which alter the primary sequence of the peptide but do not alter its secondary structure or diminish its amyloidogenic properties.

The terms "human amylin(20-29)", "β-amyloid(1-43)" and the like refer to amino acids 20-29 of the human amylin peptide as defined in SEQ ID NO:3 or amino acids 1-43 of the β-amyloid peptide as defined in SEQ ID NO:1. In all such references, the first number listed is the amino-terminus of this peptide sequence.

β-amyloid peptide naturally occurs as a series of peptides which are 39 to 43 amino acids long, with the shorter, more soluble forms being present in cerebrovascular deposits and the longer forms being found primarily in senile plaques. F. Prelli, et al., Journal of Neurochemistry,

51:648-651 (1988). The primary structure of the 43 amino acid long peptide (β1-43) is depicted in SEQ ID NO:1:

Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln	15
Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala	30
Ile Ile Gly Leu Met Val Gly Gly Val Val Ile Ala Thr	43

Even though the full length peptide of SEQ ID NO:1: has sufficient solubility in water for the following experiments, for the purposes of convenience, a more water-soluble form of the peptide is often desired. For that reason, the following examples were performed using peptides containing just the first 40 amino acids of the β-amyloid peptide (β1-40). The sequence of this preferred peptide is SEQ ID NO:2:

Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln	15
Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala	30
Ile Ile Gly Leu Met Val Gly Gly Val Val	40

It is understood by those in the art that other fragments of β-amyloid peptide, comprising amino-truncated, carboxy-truncated, or internal deletions, or any combination of these, may be employed in this invention so long as that peptide fragment demonstrates the requisite neurotoxicity.

Amylin is a 37 amino acid peptide having the primary sequence

Lys Cys Asn Thr Ala Thr Cys Ala Thr Gln Arg Leu Ala Asn Phe	15
Leu Val His Ser Ser Asn Asn Phe Gly Ala Ile Leu Ser Ser Thr	30
Asn Val Gly Ser Asn Thr Tyr	37

hereinafter referred to as SEQ ID NO:3.

The peptide β_2-microglobulin has a molecular weight of about 11,000 Daltons. It can be readily purified from urine samples using known techniques. See, e.g., I. Berggard, et al., Journal of Biological Chemistry, 243:4095 (1968).

"C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *t*-butoxy, pentoxy and the like. The term "C_1-C_6 alkoxy" includes within its definition the term "C_1-C_4 alkoxy".

As used herein, the term "C_1-C_6 alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl. The term "C_1-C_6 alkyl" includes within its definition the term "C_1-C_4 alkyl".

The current invention concerns the discovery that a select group of substituted benzofurans, benzothiophenes, indoles, naphthalenes, and dihydronaphthalenes, those of Formula I, are useful as in treating or preventing physiological disorders associated with an amyloidogenic peptide.

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius; "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "ml" means milliliter or milliliters; "M" refers to molar or molarity; "MS" refers to mass spectrometry; "IR" refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

As used herein, the term "C_1-C_{10} alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 10 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl. The term "C_1-C_{10} alkyl" includes within its definition the terms "C_1-C_4 alkyl" and "C_1-C_6 alkyl".

"C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy,

ethoxy, propoxy, isopropoxy, butoxy, *t*-butoxy, pentoxy and the like. The term "C_1-C_6 alkoxy" includes within its definition the term "C_1-C_4 alkoxy".

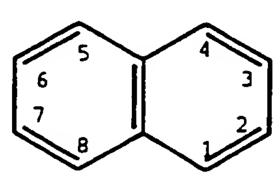
"C_1-C_6 alkylidenyl" refers to a straight or branched, divalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methylenyl, ethylenyl, propylenyl, isopropylenyl, butylenyl, isobutylenyl, *t*-butylenyl, pentylenyl, isopentylenyl, hexylenyl, and the like. The term "C_1-C_4 alkylidenyl" is encompassed within the term "C_1-C_6 alkylidenyl".

The term "halo" encompasses chloro, fluoro, bromo and iodo.

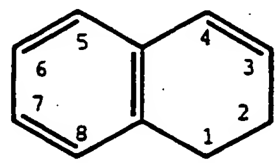
The term "leaving group" as used herein refers to a group of atoms that is displaced from a carbon atom by the attack of a nucleophile in a nucleophilic substitution reaction. The term "leaving group" as used in this document encompasses, but is not limited to, activating groups.

The term "activating group" as used herein refers a leaving group which, when taken with the carbonyl (-C=O) group to which it is attached, is more likely to take part in an acylation reaction than would be the case if the group were not present, as in the free acid. Such activating groups are well-known to those skilled in the art and may be, for example, succinimidoxy, phthalimidoxy, benzotriazolyloxy, benzenesulfonyloxy, methanesulfonyloxy, toluenesulfonyloxy, azido, or -O-CO-(C_4-C_7 alkyl).

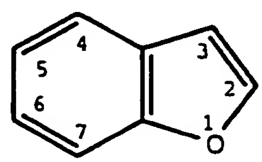
Many of the compounds employed in the present invention are derivatives of naphthalene which are named and numbered according to the RING INDEX, The American Chemical Society, as follows.



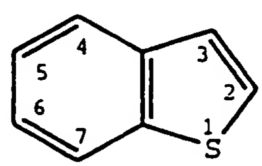
In a similar manner some of the compounds employed in the present invention are derivatives of 1,2-dihydronaphthalene which are named and numbered according to the RING INDEX as follows.



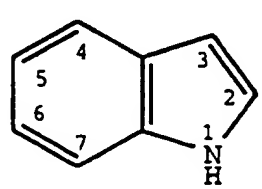
Many of the compounds of the present invention are derivatives of benzofuran which are named and numbered according to the RING INDEX, The American Chemical Society, as follows.



Some of the compounds of the present invention are derivatives of benzo[b]thiophene which are named and numbered according to the RING INDEX as follows.



In a similar manner some of the compounds of the present invention are derivatives of indole which are named and numbered according to the RING INDEX as follows.



The more preferred compounds employed in the methods of this invention are those compounds of Formula I wherein

a) A is -O-, -S-, $-CH_2-CH_2-$, or -CH=CH-;

b) R is hydrogen, hydroxy, C_1-C_3 alkoxy, or $-OSO_2-(C_1-C_{10}$ alkyl);

c) R^1 is hydrogen, hydroxy, C_1-C_3 alkoxy, or $-OSO_2-(C_1-C_{10}$ alkyl);

d) X is a bond or methylene; and

e) R^2 is piperidinyl, hexamethyleneiminyl, pyrrolidinyl, or $-NR^4R^5$, where R^4 and R^5 are C_1-C_4 alkyl; and the pharmaceutically acceptable acid addition salts and solvates.

The most preferred compounds employed in the methods of this invention are those compounds of Formula I wherein

a) A is -S-;

b) R is hydrogen, hydroxy, C_1-C_3 alkoxy, or $-OSO_2-(C_1-C_{10}$ alkyl);

c) R^1 is hydrogen, hydroxy, C_1-C_3 alkoxy, or $-OSO_2-(C_1-C_{10}$ alkyl);

d) X is a bond or methylene; and

e) R^2 is piperidinyl, hexamethyleneiminyl, pyrrolidinyl, or $-NR^4R^5$, where R^4 and R^5 are C_1-C_4 alkyl; and

f) at least one of R and R^1 is $-OSO_2-(C_1-C_{10}$ alkyl); and the pharmaceutically acceptable acid addition salts and solvates thereof.

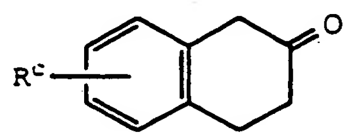
The compounds of the present invention can be prepared by a variety of procedures well known to those of ordinary skill in the art. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

A. Preparation of Dihydronapthalenyl Compounds

The compounds employed in the present invention in which A is $-CH_2-CH_2-$ or -CH=CH- may be prepared essentially as described in U.S. Patent 4,230,862, issued to T. Suarez and C.D. Jones on October 28, 1990, which is herein incorporated by reference.

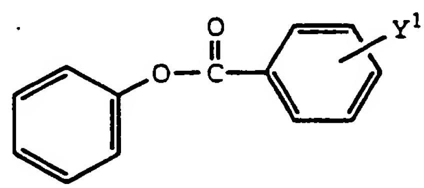
These compounds are generally prepared by the following sequences, the dihydronaphthalene structures in general being precursors to the napththalene compounds.

The naphthalenes and dihydronaphthalenes employed in the methods of the instant invention may be prepared by reacting a tetralone of Formula II



II

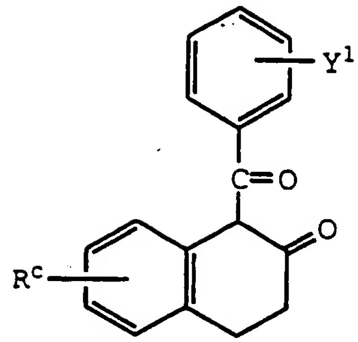
in which R^c is hydrogen, C_1-C_6 alkoxy, or benzyloxy with a phenyl benzoate of Formula III



III

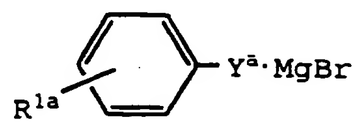
in which Y^1 is methoxy, benzyloxy, or $-O-(CH_2)_n-NR^aR^b$, where n is 1-6, and $-NR^aR^b$ is R^2. This reaction is generally carried out in the presence of a moderately strong base such as sodium amide and at room temperature or below.

The product which is obtained is a substituted tetralone of Formula IV.



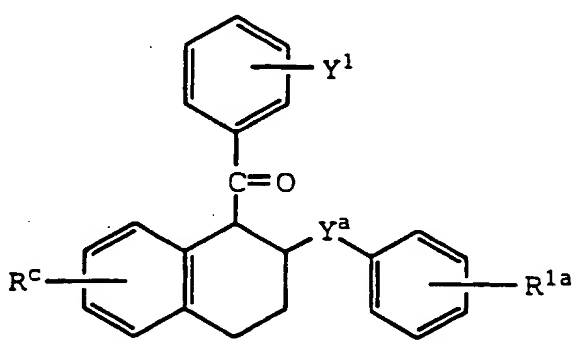
IV

This substituted tetralone is then reacted under Grignard reaction conditions with the Grignard reagent of the formula



in which R^{1a} is hydrogen, C_1-C_6 alkoxy, or benzyloxy and Y^a is a bond, methylene, or ethylene.

The compounds which are produced, a 3-phenyl-4-aroyl-1,2-dihydronaphthalenes, have the following formula, Formula V.



V

In those instances in which Y^1 is methoxy, a compound of Formula V can be treated with pyridine hydrochloride at reflux to produce the corresponding hydroxy compound. Under these conditions, should R^c or R^{1a} be alkoxy

or benzyloxy, these groups will also be cleaved, resulting in hydroxy groups.

In those instances in which Y^1 is methoxy or benzyloxy, and R^c or R^{1a} is alkoxy or benzyloxy, the group at Y^1 can be selectively cleaved by treating a compound of Formula V with an equivalent of sodium thioethoxide in N,N-dimethylformamide at a moderately elevated temperature of about 80°C to about 90°C. The process of the selective cleavage may be monitored by periodic thin layer chromatography analysis. The reaction is complete when little or no starting material remains.

Once the compound of Formula V in which Y^1 has been converted to hydroxy has been generated, that compounds can then be treated with a compound of Formula VII

$$L\text{-}(CH_2)_n\text{-}NR^aR^b$$

VII

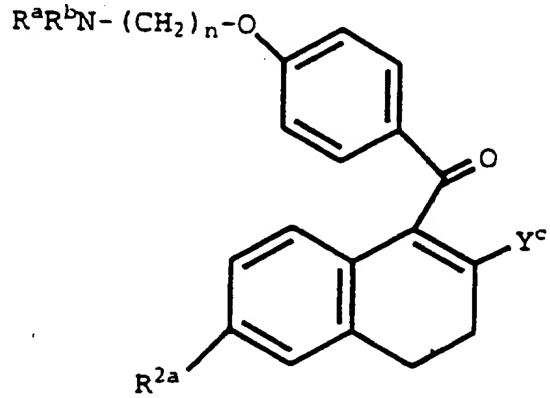
wherein L is a good leaving group such as halo, especially chloro. Under the usual reaction conditions, of course, alkylation will be effected at each of the unprotected hydroxy groups which are present in the molecule. This can be avoided, and alkylation at the 4-benzoyl groups alone can be achieved, by carrying out the reaction in the presence of an excess of finely powdered potassium carbonate and using an equivalent or slight excess of the compound of Formula VII.

Depending upon the intended structure of the final product, the compound containing the substituent of Formula VII can then be further treated with an additional quantity of sodium thioethoxide in N,N-dimethylformamide as aforedescribed to effect cleavage of any remaining alkoxy or benzyloxy groups, thereby providing another sequence for achieving formation of those compounds employed in this invention in which R^1 and/or R^2 are hydroxy.

In any of the above, it is evident that the particular sequence of synthetic steps designed to produce a compound having substituents of particular definition and

location is such as one of ordinary skill in the art will well recognize.

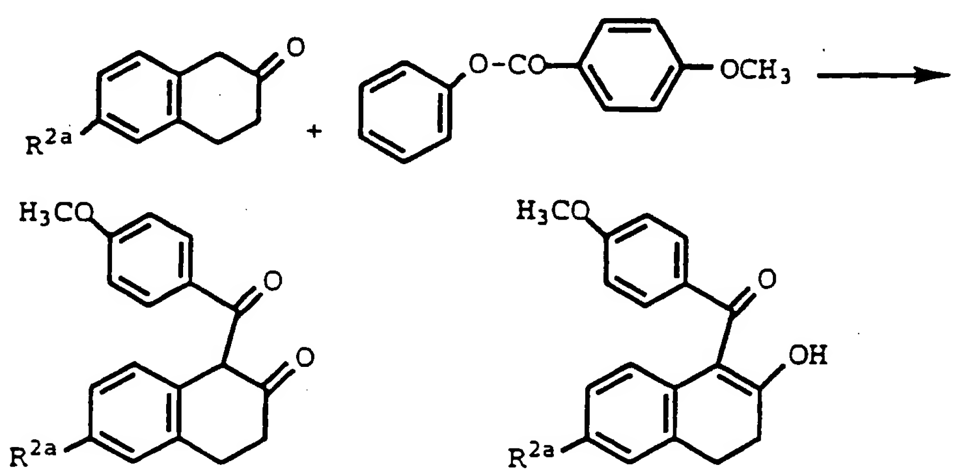
In another route for preparing the compounds of Formula I, compounds of Formula VI



VI

wherein: R^{2a} is -H or C_1-C_6 alkoxy; and Y^c is C_1-C_6 alkoxy-substituted phenyl or benzyl, are prepared essentially as described by C.D. Jones, et al., Journal of Medicinal Chemistry, 53:931-938 (1992), which is herein incorporated by reference.

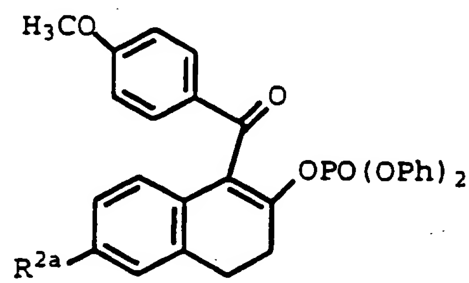
Generally, a tetralone, as described above, or a salt thereof, is acylated using standard Friedel Crafts conditions to provide a highly enolized diketone of formula VIa



VIa

wherein R^{2a} is -H or C_1-C_6 alkoxy.

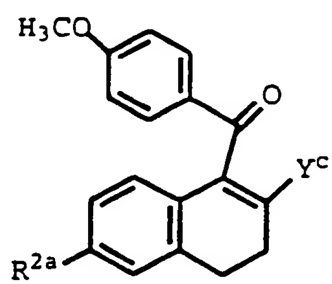
Subsequent derivatization using sodium hydride, followed by the addition of diphenyl chlorophosphate, gives the enol phosphate derivative tentatively assigned the Formula VIb



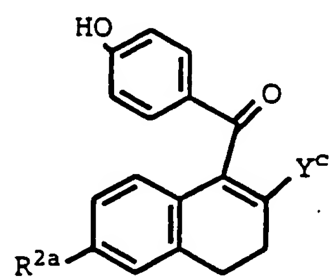
VIb

wherein R^{2a} is as defined above.

Addition of phenyl- or benzyl-, substituted phenyl- or substituted benzylmagnesium bromide to a compound of formula VIb, and subsequent selective demethylation provide compounds of formula VIc and VId, respectively, as described by Jones, supra.



VIc



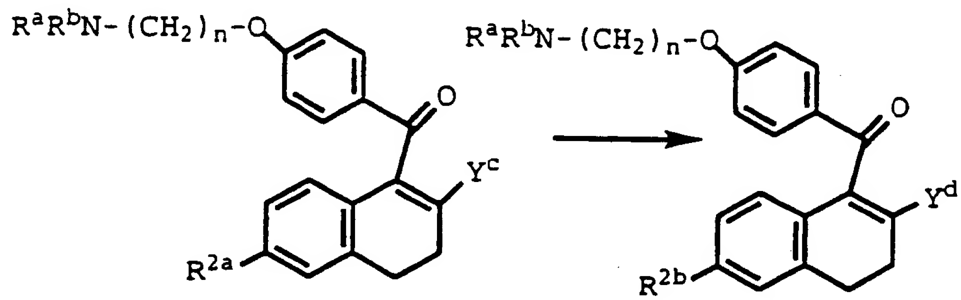
VId

wherein R^{2a} and Y^c are as defined above.

Finally a compound of formula VId is alkylated with a compound of the formula

$$L-(CH_2)_n-NR^aR^b$$

in which L is a bromo or, preferably, a chloro moiety, and R^{2a} and Y^c optionally are dealkylated by standard procedures, to provide compounds of formulae VIe and VIf, respectively.



VIe VIf

wherein R^{2b} is -H or -OH and Y^d is phenyl, benzyl, hydroxyphenyl, or hydroxybenzyl.

In the process for preparing compounds of formula VIe or VIf, it is evident that the particular sequence of synthetic steps designed to produce a compound having substituents of particular definition and location is such as one of ordinary skill in the art will recognize.

The compounds of Formula VIf can be substituted using standard means, if desired, to produce the corresponding dihydronaphthenyl compounds of Formula I.

B. Preparation of Napthalenyl Compounds

Those compounds of Formula I which are substituted naphthalenes are readily prepared from the corresponding dihydronaphthalenyl compounds. Selective dehydrogenation of the dihydronaphthalene structure to produce specifically the corresponding naphthalene can be accomplished by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at a temperature of from about 50°C to about 100°C. The naphthalene which is produce may be further converted to other naphthalene compounds by means of the derivatizing reactions described <u>supra</u>.

Example 1

Preparation of 3-(4-methoxyphenyl)-4-[4-(2-pyrrolidin-1-ylethoxy)benzoyl-1,2-dihydronaphthalene, citrate salt

The title compound was prepared as described in United States Patent 4,230,862. To a suspension of sodium amide (15.2 g, 0.38 mol) in 250 ml of tertrahydrofuran were added 50 grams (0.34 mol) of β-tetralone. The mixture was stirred for 15-20 minutes, and 78 grams of phenyl *p*-methoxybenzoate dissolved in tetrahydrofuran were added. The temperature of the reaction mixture was maintained below 10°C, and the mixture was then stirred at room temperature overnight. The reaction mixture was concentrated and the water was added to the residue. The aqueous mixture was extracted with ethyl acetate, and the ethyl acetate extract was washed and concentrated.

The residue was chromatographed on silica using benzene as eluant. The purer fractions obtained by the chromatographic separation were combined and concentrated, and the residue was dissolved in a minimum of methanol. The methanol was cooled, and 35.2 grams of 1-(4-methoxybenzoyl)-2-tetralone were collected by filtration.

4-Bromoanisole (18.7 g, 0.1 mol) was added dropwise in ether to tetrahydrofuran containing 5 drops of 1,2-dibromoethane and 3.6 grams (0.15 mol) of magnesium. Reaction occurred almost immediately, and the addition was continued at a slow rate with evolution of heat sufficient to maintain a general reflux. Upon completion of the addition, the above substituted β-tetralone dissolved in acetone was added dropwise with stirring over a two hour period, the mixture being maintained at 40°C. The resulting mixture was then poured into cold, dilute hydrochloric acid, and the acidic mixture was extracted with ethyl acetate. The ethyl acetate extract was washed, dried, and concentrated to an oil. The oil was chromatographed over silica using benzene as eluant. A subsequent elution of the column with a mixture

of benzene containing two percent ethyl acetate yielded 15 grams of 3-(4-methoxyphenyl)-4-(4-methoxybenzoyl)-1,2-dihydronaphthalene as an oil.

A mixture of 11.1 grams (0.03 mol) of the above dimethoxy product, 7.2 grams of sodium hydride (50 percent in oil), and 11 ml of ethyl mercaptan in N,N-dimethylformamide was prepared. The mixture was heated to 65-70°C and maintained at that temperature for about two hours. The mixture was then cooled and conetrated. The concentrate was acidified and extracted with ethyl acetate. The ethyl acetate extract was washed, dried, and evaporated. The residue was dissolved in benzene and chromatographed over silica to obtain five grams of an oil comprising relatively pure 3-(4-methoxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene.

The above phenolic product (4.3 g, 0.01 mol) was dissolved in N,N-dimethylformamide. To this solution was added 0.7 grams of sodium hydride (50 percent in oil), and the resulting mixture was warmed to 40°C for one hour and then was cooled to room temperature. To the mixture then were added 1.6 grams of 1-chloro-2-pyrrolidinylethane, and the mixture was warmed to 60°C and maintained at this temperature for about two hours. The reaction mixture was then stirred at room temperature overnight.

The mixture was concentrated, and water was added to the residue. The aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed and concentrated to a residue. The residue was extracted with hexanes, the insoluble portion was dissolved in ethyl acetate, and the ethyl acetate solution was extracted with 1 N hydrochloric acid. The acid extract was rendered alkaline, and then was extracted with ethyl acetate. The ethyl acetate extract was washed and concentrated. One equivalent of citric acid in acetone then was added to the concentrate, and the mixture was concentrated to dryness. The residue was dissolved in a large volume of methyl ethyl ketone. The ketone solution was concentrated to about 300 ml and was

cooled to 0°C. The title product, the citrate salt of 3-(4-methoxyphenyl)-4-[4-(2-pyrrolidin-1-ylethoxy)benzoyl-1,2-dihydronaphthalene, was collected by filtration and vacuum dried. mp 82-85°C.

Analysis for $C_{36}H_{39}NO_{10}$:

Theory: C, 66.96; H, 6.09; N, 2.17; O, 24.78.

Found: C, 66.70; H. 6.27; N, 2.27; O, 24.54.

Example 2

Preparation of 3-phenyl-4-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-7-methoxy-1,2-dihydronaphthalene.

The title product was prepared as described iin United States Patent 4,230,862. To 300 ml of N,N-dimethylformamide were added 107 grams of phenyl *p*-hydroxybenzoate and 26 grams of sodium hydride (50 percent in oil). The mixture was heated to 60°C and maintained at this temperature for about two hours. To this mixture was added 1-chloro-2-pyrrolidin-1-ylethane (67 g), and the mixture was stirred overnight at 85°C. The bulk of the N,N-dimethylformamide then was evaporated from the mixture. Water was added to the residue, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was concentrated, and the residue was dissolved in a 1:1 mixture of ether and ethyl acetate. The organic solution was then extracted with 2 N hydrochloric acid, and the acid extract was added dropwise to 2 N sodium hydroxide. The resulting mixture was extracted with ethyl acetate, and the ethyl acetate extract was washed and then dried over magnesium sulfate. The ethyl acetate was concentrated to obtain 110 grams of crude phenyl p-(2-pyrrolidin-1-ylethoxy)benzoate.

To a suspension of 20 grams (0.5 mol) of sodium amide in tetrahydrofuran were added dropwise 41.7 grams of 6-methoxy-2-tetralone in tetrahydrofuran, the temperature of the mixture being maintained below 10°C. Upon completion of the addition, the mixture was stirred for 20 minutes, the

reaction mixture being maintained below 10°C, after which time an exothermic reaction occurred, the reaction temperature rising to about 20°C.

The above prepared phenyl *p*-(2-pyrrolidin-1-ylethoxy)benzoate, dissolved in tetrahydrofuran, was then added dropwise, and the mixture was stirred overnight at room temperature. The mixture was poured into water, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate extract was washed several times with water, and dried over magnesium sulfate. The ethyl acetate was concentrated to obtain about 100 grams of crude material which was dissolved in 1.5 liters of acetone, and one equivalent of citric acid in 400 ml of ethyl acetate was added. The resulting solid was isolated by filtration and vacuum dried to obtain 85.9 grams of 6-methoxy-1-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-2-tetralone. The product was then chromatographed over silica using ethyl acetate as eluant, and the citrate salt was prepared from the recovered product.

The above product (8.6 g, 0.02 mol) was added to a solution of phenylmagnesium bromide in tetrahydrofuran. The resulting mixture was stirred for one hour at room temperature and then was warmed to 50°C and maintained at this temperature for three hours. The resulting mixture was poured into a mixture of ice and hydrochloric acid, and the acid mixture was extracted with ethyl acetate. The ethyl acetate extract was washed, dried, and concentrated to obtain 10.5 grams of a red-brown oil. The oil was added to 500 ml of acetic acid, and the mixture was heated on a steam bath for about 30 minutes. The acid was stripped off, and water as added to the residue.

The aqueous mixture was rendered alkaline by addition of base, and the alkaline mixture was extracted with ethyl acetate. The extract was dried and concentrated to obtain 8.7 grams of product which was dissolved in acetone, and one equivalent of citric acid was added to the mixture. The acetone was stripped off, and methyl ethyl ketone was

added to the residue. The mixture was maintained at 0°C overnight, and the crystals which formed were collected by filtration and washed with cold methyl ethyl ketone and vacuum dried. The solid was recrystallized from acetone to obtain the title compound in the form of its citrate salt. mp 98-100°C.

Analysis of $C_{36}H_{39}NO_{10}$:

Theory: C, 66.96; H, 6.09; N, 2.17; O, 24.78.
Found: C, 66.72; H, 6.27; N, 2.09; O, 24.50.

The title compound in the form of its free base was generated by treatment of the citrate salt with dilute alkali.

Analysis for $C_{30}H_{31}NO_5$:

Theory: C, 79.44; H, 6.89; N, 3.09.
Found: C, 79.19; H, 6.68; N, 2.91.

Example 3

Preparation of 3-phenyl-4-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-1,2-dihydronaphthalene

The title product was prepared as described in United States Patent 4,230,862. To a solution of 5.0 grams (18 mmol) of 1-(4-methoxybenzoyl)-2-tetralone (prepared as described in Example 1) in 50 ml of ether was added dropwise at 0°C a solution of phenylmagnesium bromide (18 mmol) in 9 ml of ether. Upon completion of the addition, the mixture was stirred for twenty minutes. Thin layer chromatography of the reaction mixture indicated the presence of starting material. An additional 13.5 ml of the phenylmagnesium bromide solution were added.

The mixture was refluxed for two hours and then was cooled and poured over iced aqueous ammonium chloride solution. The organic layer was separated and washed with brine. The mixture was then dried over magnesium sulfate, filtered, and evaporated to give about ten grams of a yellow

oil. After a wash with hexanes, the product was further purified by chromatography to give 4.67 grams of 3-phenyl-4-(4-methoxybenzoyl)-1,2-dihydronaphthalene.

To 2.0 grams (6 mmol) of the above dihydronaphthalene, dissolved in 10 ml of N,N-dimethylformamide, were added sodium thioethoxide (7.5 mmol), dissolved in 15 ml of N,N-dimethylformamide. The addition was carried out under a nitrogen atmosphere and at 80°C. The mixture was maintained at 80°C for fifteen hours. The mixture was then cooled and poured into an iced aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate, and the ethyl acetate extract was washed four times with brine.

The ethyl acetate extract was dried over magnesium sulfate an evaporated to give an oil which was further purified by chromatography on a silica column, using benzene to elute impurities. The product was then eluted with ethyl acetate to give, upon evaporation of the ethyl acetate, 1.69 grams of 3-phenyl-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene as a clear pale yellow oil.

A mixture of 1.61 grams (4.95 mmol) of the above product in 10 ml of dry N,N-dimethylformamide containing 119 mg (4.95 mmol) of sodium hydride and freshly distilled 1-chloro-(2-pyrrolidin-1-yl)ethane. The addition was made under a nitrogen atmosphere with the temperature being maintained at about 10°C. Upon completion of the resulting efferverscence, the mixture was heated to 80°C and maintained at that temperature for about two hours. The mixture was then poured into water, and the total was extract with ether. The ether extract was washed five times with brine, and dried over magnesium sulfate. The ether layer was then filtered and evaporated to give a gray oil, which was further purified by chromatography to give 3-phenyl-4-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-1,2-dihydronaphthalene.

The product was converted to the corresponding citrate salt by treatment with 0.59 grams of citric acid in 50 ml of hot acetone. The resulting mixture was evaporated

to dryness, and the residue was stirred for about fifteen hours with ether to obtain the citrate salt. mp 89-93°C.
Analysis for $C_{33}H_{37}NO_9 \cdot 0.5\ H_2O$:

Theory: C, 67.34; H, 6.13; N, 2.25.
Found: C, 67.06; H, 6.41; N, 2.66.

Example 4

Preparation of 1-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-2-phenylnaphthalene, citrate salt

The title product was prepared as described in United States Patent 4,230,862. To 30 ml of dioxane were added 3-phenyl-4-(4-methoxybenzoyl)-1,2-dihydronaphthalene (1.90 g, 5.58 mmol), prepared as described in Example 3, *supra*, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.00 g, 8.81 mmol). The resulting mixture was heated to reflux and refluxed for twelve hours under a nitrogen atmosphere. The mixture was then cooled and evaporated to dryness. The residue was partitioned between ether and water. The organic fraction was washed 5 N sodium hydroxide (5 x 20 ml), followed by a wash with brine. The mixture was then dried over magnesium sulfate and evaporated to give 1.9 grams of substantially pure 1-(4-methoxybenzoyl)-2-phenylnaphthalene.

Employing substantially the same demethylation procedure as described in Example 3, 1.83 grams (5.41 mmol) of the above product were treated with sodium thioethoxide to obtain 1.4 grams of 1-(4-hydroxybenzoyl)-2-phenylnaphthalene.

To 10 ml of N,N-dimethylformamide were added 1.25 grams of the above product. The resulting mixture was added at about 10°C to a mixture of 20 ml of N,N-dimethylformamide containing 120 mg (5.0 mmol) of sodium hydride and 800 mg of 1-chloro-2-(pyrrolidin-1-yl)ethane. Upon completion of the resulting effervescence, the mixture was heated to 80°C and maintained at that temperature for about three hours, during which time sodium chloride precipitated. The mixture was cooled and evaporated to dryness. The resulting residue was

partitioned between water and ethyl acetate. The organic fraction was washed with brine (5 x 25 ml). The organic fraction was dried and evaporated to give 1.62 grams of 1-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-2-phenylnaphthalene as a yellow oil.

The above free base was converted to the corresponding citrate salt in accordance with the method of Example 3, employing 0.811 grams of citric acid hydrate. The title compound was obtained as an amorphous solid which crystallized on standing overnight in ether. mp 105-108°C. Analysis for $C_{33}H_{35}NO_9 \cdot H_2O$:

Theory: C, 65.55; H, 5.90; N, 2.22.
Found: C, 66.90; H, 5.85; N, 2.25.

Example 5

Preparation of 3-(4-methoxyphenyl)-4-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, citrate salt.

The title compound was prepared as described in United States Patent 4,230,862. To a suspension of sodium hydride (0.269 g, 11 mmol), washed free of mineral oil, and 1-chloro-2-(piperidin-1-yl)ethane (1.82 g, 12 mmol) in N,N-dimethylformamide (50 ml) at 0°C, and under a nitrogen atmosphere, were added 4.0 grams (10 mmol) of 3-(4-methoxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene, prepared as described in Example 1, dissolved in 20 ml of N,N-dimethylformamide. The solution was added dropwise with stirring. When the effervescence had ceased for the most part, the mixture was heated to 50°C and maintained at that temperature for several hours. The progress of the reaction was monitored by thin layer chromatography.

Once the reaction had progressed sufficiently, the N,N-dimethylformamide was evaporated, and the concentrated mixture was poured over ice water and ethyl acetate. The ethyl acetate fraction was washed with brine, dried over potassium carbonate, filtered, and evaporated, The resulting

oil was chromatographed over a 1.5" x 12" silica column using the following as a double gradient:

(i) 10 percent ethyl acetate in benzene (500 ml) → 20 percent ethyl acetate in benzene (2 liters);
(ii) 20 percent ethyl acetate in benzene (1.5 liters) → 1:1 mixture of methanol and ethyl acetate (1.5 liters).

The appropriate fractions were concentrated to give an almost colorless oil. The oil was dissolved in ethyl acetate, and the ethyl acetate solution was dried over potassium carbonate, filtered, and evaporated to give 4.7 grams of the free base of the title compound as a pale yellow oil.

The free base (3.4 g, 7.28 mmol) was treated with citric acid monohydrate (1.49 g, 7.1 mmol) in about 20 ml of boiling acetone. When a clear solution was obtained, the acetone was evaporated, 300 ml of anhydrous ether was added, and the resulting precipitate was stirred overnight. The title compound (5.2 grams) was collected as a white powder.
Analysis for $C_{37}H_{41}NO_{10}$:

Theory: C, 67.36; H, 6.26; N, 2.12.
Found: C, 67.25; H, 5.96; N, 1.84.

Example 6

Preparation of 3-(4-methoxyphenyl)-4-[4-(2-dimethylaminoethoxy)benzoyl]-1,2-dihydronaphthalene, citrate salt.

The title compound was prepared as described in United States Patent 4,230,862. To 50 ml of acetone were added 4.0 grams (11.2 mmol) of 3-(4-methoxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene, prepared as described in Example 1, 1.81 grams (16.8 mmol) of 1-chloro-2-dimethylaminoethane (freshly prepared from the hydrohloride),

and 2.32 grams (16.8 mol) of finely powdered potassium chloride. The resulting mixture was refluxed under nitrogen with stirring for about 72 hours. The progress of the reaction was monitored by thin layer chromatography.

The resulting mixture was then poured over ice, and the resulting mixture was extracted with ether. The ether was washed three times with brine, dried over potassium carbonate, filtered, and evaporated to obtain 4.51 grams of the free base of the title compound as a brown oil.

The oil was vacuum dried and then was converted to the citrate salt by treatment with 2.17 grams (10.4 mmol) of citric acid monohydrate in 50 ml of hot acetone. Evaporation of the acetone and stirring of the residue with ether gave 5.2 grams of the title compound as an amorphous solid.

Analysis for $C_{34}H_{37}NO_{10}$:

Theory: C, 65.90; H, 6.02; N, 2.26.

Found: C, 66.17; H, 6.23; N, 2.37.

Example 7

Preparation of 3-(4-hydroxyphenyl)-4-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, mesylate salt

The title compound was prepared as described in United States Patent 4,230,862. To 25 ml of methyl ethyl ketone were 10 grams (2.92 mmol) of 3-(4-hydroxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene, 0.497 grams (2.92 mmol) of 1-chloro-2-(pyrrolidin-1-yl)ethane, and 1.21 grams (8.77 mmol) offinely powdered potassium carbonate. The resulting mixture was refluxed for 16 hours. The mixture was then cooled and poured into a mixture of water and ethyl acetate. The resulting mixture was rendered acidic by addition of 1 N hydrochloric acid and then alkaline by the addition of sodium bicarbonate.

The organic fraction was washed with brine, dried over magnesium sulfate, and evaporated to give a yellow oil. The resulting oil was further purified by chromatography.

The free base (362 mg, 0.825 mmol) as converted to the mesylate aslt by treatment with an equivalent of methanesulfonic acid in acetone to yield the title compound as an amorphous solid.

Analysis for $C_{31}H_{37}NO_6S$:

Theory: C, 67.27; H, 6.21; N, 2.61.

Found: C, 67.25; H, 6.19; N, 2.69.

Example 8

Preparation of 3-(4-methoxyphenyl)-4-[4-[2-(hexamethyleneimin-1-yl)benzoyl]-1,2-dihydronaphthalene, mesylate salt

The title compound was prepared as described in United States Patent 4,230,826. To 50 ml of methyl ethyl ketone were added 3.0 g (8.43 mmol) of 3-(4-methoxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene, 1.84 g (9.27 mmol) of 1-chloro-2-(hexamethyleneimin-1-yl)ethane hydrochloride, and 3.25 grams (25.3 mmol) of finely powdered potassium carbonate. The mixture was refluxed for 48 hours.

The mixture was then poured into water, and ethyl acetate was added. The resulting organic layer was separated, washed with brine, dried, and evaporated to a yellow oil. The oil was further purified by chromatography. The free base of the title compound was recovered (2.51 g) as a pale yellow oil. The oil was treated with 0.431 g (4.48 mmol) of methanesulfonic acid in 10 ml of acetone. Upon scratching and cooling of the mixture, crystals formed. The mixture was cooled overnight and 1.97 grams of the title compound were obtained as a white crystals. mp 123-125°C.

Analysis for $C_{34}H_{41}NO_6S$:

Theory: C, 68.61; H, 6.80; N, 2.42.

Found: C, 68.38; H, 6.62; N, 2.40.

Example 9

Preparation of 3-(4-methoxyphenyl)-4-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, mesylate salt

The title compound was prepared as described in United States Patent 4,230,862. To 150 ml of methyl ethyl ketone were added 7.8 g (21.9 mmol) of 3-(4-methoxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene, 4.84 grams (23.6 mmol) of 1-chloro-2-(piperidin-1-yl)ethane hydrochloride, and 14.5 grams (109 mmol) of potassium carbonate. The resulting mixture was refluxed overnight.

The mixture was then poured into a mixture of water and ethyl acetate. The resulting orgnaic fraction was spearated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo to obtain the free base of the title compound as a yellow oil.

The oil was dissolved in 30 ml of acetone and was treated with 2.105 grams (21.9 mmol) of methanesulfonic acid. The mixture was cooled and scratched, and the title compound was collected at -40°C and ashed well with acetone and ether cooled to about -60°C. The solid was then vacuum dried at 100°C to obtain 11.21 grams of the title compound as a white crystalline solid. mp 157-158°C.

Analysis for $C_{33}H_{39}NO_6S$:

Theory: C, 68.18; H, 6.62; N, 2.48.

Found: C, 68.11; H, 6.76; N, 2.50.

Example 10

Preparation of 3-(4-methoxyphenyl)-4-(4-diethylaminoethoxybenzoyl)-1,2-dihydronaphthalene, mesylate salt

To 75 ml of methyl ethyl ketone were added 4.0 grams (11.2 mmol) of 3-(4-methoxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene, 2.41 grams (14 mmol)

of 1-chloro-2-diethylaminoethane hydrochloride, and 7.93 grams (56 mmol) of finely powdered potassium carbonate. The mixture was refluxed overnight, and, employing the method of Example 9, 5.67 grams of the free base of the title compound were obtained as a yellow oily material.

The oil was treated with 1.07 grams (11.2 mmol) of methanesulfonic acid in about 15 ml of acetone. The resulting mixture was maintained with cooling for several days after which white crystals appeared. The crystals were somewhat hygroscopic and were collected as quickly as possible and vacuum-dried. There were obtained 4.3 grams of the title compound as a white crystalline solid.

Analysis for $C_{31}H_{39}NO_6S$:

Theory: C, 67.24; H, 7.10; N, 2.53.

Found: C, 67.48; H, 6.92; N, 2.43.

Example 11

Preparation of 3-(4-methoxyphenyl)-4-(4-diisopropylaminoethoxybenzoyl)-1,2-dihydronaphthalene, mesylate salt

To 75 ml of methyl ethyl ketone were added 3.84 grams (10.8 mmol) of 3-(4-methoxyphenyl)-4-(4-hydroxybenzoyl)-1,2-dihydronaphthalene, 2.70 grams (13.5 mmol) of 1-chloro-2-diisopropylaminoethane hydrochloride, and 7.11 grams (54 mmol) of finely powdered potassium carbonate. The mixture was allowed to reflux overnight, and, upon workup, in accordance with the procedure of Example 9, 5.64 grams of the free base of the title compound were obtained as a yellow oily substance. The oily product was treated with 1.04 grams (10.8 mmol) of methanesulfonic acid in about 25 ml of acetone. The mixture was cooled, and crystals slowly appeared. The crystals collected at -40°C with the aid of acetone cooled to -60°C. Vacuum drying of the product gave 5.1 grams.

Analysis for $C_{33}H_{41}NO_6S$:

Theory: C, 68.37; H, 7.31; N, 2.42.
Found: C, 68.08; H, 6.91; N, 2.21.

The following compounds were prepared essentially as described in the above examples:

Example 12

3-hydroxy-4-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, sodium salt

Example 13

2-(4-methoxyphenyl)-1-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]naphthalene, mesylate salt

Example 14

3-(4-methoxyphenyl)-4-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-7-methoxy-1,2-dihydronaphthalene, mesylate salt

Example 15

3-(4-methoxyphenyl)-4-[4-(2-dimethylaminoethoxy)benzoyl]-1,2-dihydronaphthalene, 2-hydroxy-1,2,3-propanetricarboxylic acid salt

Example 16

3-(4-methoxyphenyl)-4-[4-[2-(N-methyl-1-pyrrolidinium)ethoxy]benzoyl]-1,2-dihydronaphthalene, iodide salt

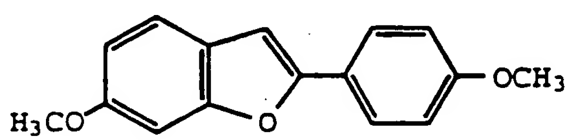
Example 17

3-(4-methoxyphenyl)-4-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, mesylate salt

C. Preparation of Indoles, Benzofurans and Benzothiophenes

The benzofurans, benzothiophenes and indoles employed in the methods of the instant invention were made essentially as described in United States Patents 4,133,814, issued January 9, 1979, 4,418,068, issued November 29, 1983, and 4,380,635, issued April 19, 1983, all of which are herein incorporated by reference. This process provides a convenient process which acylates a methylated starting compound and then optionally demethylates it to obtain the desired dihydroxy product. The acylation and demethylation may be performed in successive steps in a single reaction mixture or the intermediate may be isolated and the demethylation step be performed in a separate reaction.

The methyl-protected compound of Formula VII



VII

is most easily obtained by reacting 3-methoxyphenol and α-bromo-4-methoxyacetophenone in the presence of a strong base at a relatively low temperature, to form α-(3-methoxyphenoxy)-4-methoxyacetophenone, which is then ring closed with an agent such as polyphosphoric acid at a high temperature to obtain the intermediate compound of Formula VII.

The acylation of this invention is a Friedel-Crafts acylation, and is carried out in the usual way, using aluminum chloride or bromide, preferably the chloride, as the acylation catalyst.

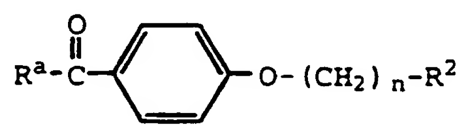
The acylation is ordinarily carried out in a solvent, and any inert organic solvent which is not significantly attacked by the conditions may be used. For

example, halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform, and the like may be used, as can aromatics such as benzene, chlorobenzene, and the like. It is preferred to use a halogenated solvent, especially dichloromethane.

It has been found that toluene is rather easily acylated under the conditions used in the Friedel-Crafts acylation, and so it is important, when toluene is used in an earlier step of the process, to remove it as completely as possible from the protected starting compound, to avoid wasting the acylating agent.

The acylations may be carried out at temperatures from about -30°C to about 100°C, preferably at about ambient temperature, in the range of from about 15°C to about 30°C.

The acylating agent is an active form of the appropriate benzoic acid of Formula VIII



VIII

wherein R^a is chloro or bromo. The preferred acylating agents are those wherein R^a is chloro. Thus, the most highly preferred individual acylating agents are 4-[2-(piperidin-1-yl)ethoxy]benzoyl chloride, 4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl chloride, 4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl chloride, 4-[2-(dimethylamino)ethoxy]-benzoyl chloride, 4-[2-(diethylamino)ethoxy]benzoyl chloride, and 4-[2-(diisopropylamino)ethoxy]benzoyl chloride.

The acyl chloride used as an acylating agent may be prepared from the corresponding carboxylic acid by reaction with a typical chlorinating agent such as thionyl chloride. Care must be taken to remove any excess chlorinating agent from the acyl chloride. Most conveniently, the acyl chloride is formed <u>in situ</u>, and the excess chlorinating agent is distilled off under vacuum.

It is generally preferred that an equimolar amount of the compounds of Formula VII and VIII are reacted together. If desired, a small excess of either reactant may be added to assure the other is fully consumed. It is generally preferred to use a large excess of the acylation catalyst, such as about 2-12 moles per mole of product, preferably about 5-10 moles of catalyst per mole of product.

The acylation is rapid. Economically brief reaction times, such as from about 15 minutes to a few hours provide high yields of the acylated intermediate. Longer reaction times may be used if desired, but are not usually advantageous. As usual, the use of lower reaction temperatures call for relatively longer reaction times.

The acylation step is ended and the optional demethylation step is begun by the addition of a sulfur compound selected from the group consisting of methionine and compounds of the formula

$$X^1\text{-S-}Y^\alpha$$

wherein X^1 is hydrogen or unbranched C_1-C_4 alkyl, and Y^α is C_1-C_4 alkyl or phenyl. The sulfur compounds are, preferably, the alkylthiols, such as methanethiol, ethanethiol, isopropanethiol, butanethiol, and the like; dialkyl sulfides, such as diethyl sulfide, ethyl propyl sulfide, butyl isopropyl sulfide, dimethyl sulfide, methyl ethyl sulfide, and the like; benzenethiol; methionine; and alkyl phenyl sulfides, such as methyl phenyl sulfide, ethyl phenyl sulfide, butyl phenyl sulfide, and the like.

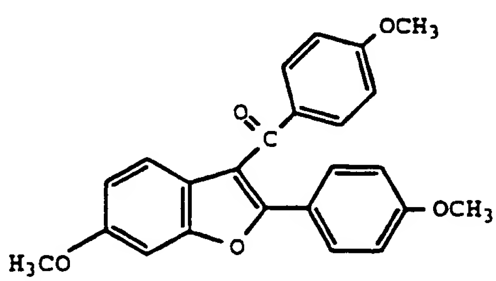
It has been found that demethylation is most efficient when a substantial excess of the sulfur compound is used, in the range of about 4 to about 10 moles per mole of the starting benzofuran. The process may be carried out, although less efficiently, with a smaller amount of the sulfur compound (in the range of about 2 to 3 moles per mole of the starting compound). It is also possible to use a small amount of the sulfur compound, and to improve the yield

by the addition of about 1 to 3 moles of an alkali metal halide, such as sodium, potassium, or lithium chloride, bromide, or iodide.

The demethylation reaction goes well at about ambient temperature, in the range of from about 15°C to about 30°C, and such operation is preferred. The demethylation may be carried out, however, at temperatures in the range of from about -30°C to about 50°C if it is desired to do so. Short reaction times, in the range of about one hour, have been found to be sufficient.

After the product has been demethylated, it is recovered and isolated by conventional means. It is customary to add water to decompose the complex of the acylation catalyst. Addition of dilute aqueous acid is advantageous. The product precipitates in many instances, or may be extracted with an organic solvent according to conventional methods. The examples below further illustrate the isolation.

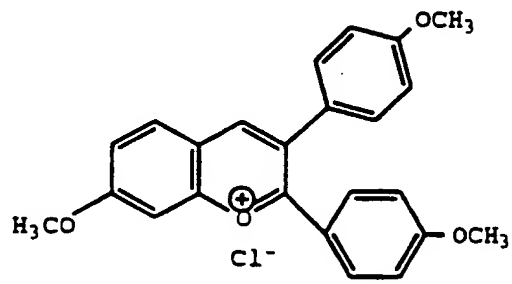
In an alternative process an intermediate compound of Formula IX



IX

is synthesized by the reaction of 2-hydroxy-4-methoxybenzaldehyde and 1-(4-methoxyphenyl)-2-(4-methoxyphenyl)ethanone, essentially as described in Preparation 3a, *infra*. This reaction usually employs equimolar amounts of the two reactants although other ratios are operable. The reaction is performed in a non-reactive solvent such as ethyl acetate, chloroform, and the like, in the presence of an acid. Hydrochloric acid, particularly

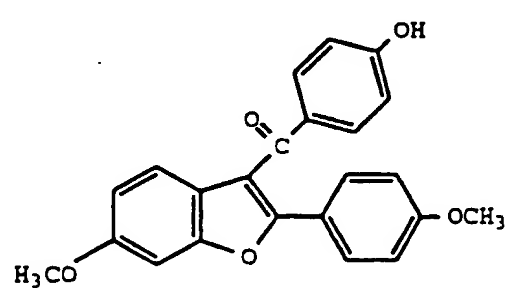
when created by bubbling anhydrous hydrogen chloride, is an especially preferred acid. Lower alkyl alcohols are usually added to the non-polar solvent so as to retain more of the hydrochloric acid created _in situ_, with ethanol and methanol being especially preferred. The reaction is performed at temperatures ranging from ambient temperature up to the reflux temperature of the mixture. This reaction results in the synthesis of a compound of Formula X



X

or an equivalent anion if hydrochloric acid is not used, which is then oxidized to the compound of Formula IX by the addition of hydrogen peroxide. The intermediate of Formula X may be isolated or may preferably be converted to the compound of Formula IX in the same reaction vessel.

The compound of Formula IX is then selectively demethylated, essentially as described in Preparation 4a, _infra_ to yield the compound of Formula XI



XI

The ether of the compounds of Formula I is then produced by the substitution of the hydrogen on the hydroxy group by an alkyl or halide.

Those compounds of Formula I in which "A" equals $-N(R^{11})-$ are prepared in essentially the same manner as the substituted benzofurans described _supra_. Example 33, _infra_, provides one such protocol for synthesizing the substituted indoles of this invention.

Those compounds of Formula I in which "A" equals $-S(O)_m-$ are prepared in essentially the same manner as the substituted benzofurans described _supra_. The examples _infra_ provide several exemplifications of these benzothiophenes and the oxidated derivatives thereof.

Those compounds of Formula I in which m is one or two may be prepared by oxidation of the corresponding benzothiophene in which m is zero. Oxidation may be carried out by treating the benzothiophene with an oxidizing agent, for example, m-chloroperbenzoic acid, or the like, for a time sufficient to achieve formation of the sulfoxide group. The progress of the oxidation reaction may be monitored by thin layer chromatography methods.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, caprate, caprylate, cinnamate, citrate,

formate, fumarate, glycollate, heptanoate, hippurate, hydrochloride, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferable salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of Formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides and carbonates, as well as aliphatic and aromatic amines, aliphatic diamines and hydroxy alkylamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, calcium hydroxide, methylamine, diethylamine, ethylene diamine, cyclohexylamine and ethanolamine.

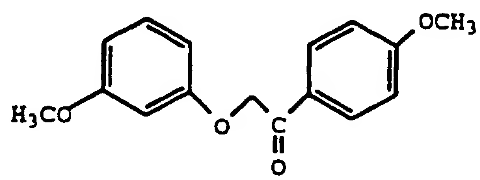
The pharmaceutically acceptable salts frequently have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Examples

The following experiments illustrate the preparation of the benzofurans, benzothiophenes and indoles employed in the present invention. The terms "NMR", "IR" or "MS" following a synthesis protocol indicates that the nuclear magnetic resonance spectrum, infrared spectrum, or the mass spectrometry was performed and was consistent with the title product.

Preparation 1a

Synthesis of 2-(3-methoxyphenoxy)-1-(4-methoxyphenyl)ethanone.



In a one liter round-bottom flask, fitted with a condenser and nitrogen inlet, were added 3-methoxyphenol (12.4 g, 0.1 mole), 4-methoxyphenacyl bromide (22.9 g, 0.1 mole), potassium carbonate (17.3 g, 0.125 mole) in 100 ml of 2-butanone. This mixture was heated to 80°C and was maintained at this temperature for about four hours. The progress of the reaction was monitored by thin layer chromatography (silica gel, 9:1 toluene:ethyl acetate).

After the four hours at 80°C the reaction mixture was cooled and the reaction mixture was partitioned by the addition of water. The organic phase was removed and the aqueous layer was washed with 2-butanone. The organic layers were then combined, dried over magnesium sulfate, and the solvents were removed in vacuo to yield 31.1 grams of a yellow oil. The yellow oil was further purified by chromatography, the fractions containing the desired product were then crystallized. All of the crystalline fractions

were combined and then dissolved in 80 ml of hot ethanol. Fifteen milliliters of hot water was then added, the product was crystallized, and subsequently washed with an ethanol/water mixture to yield 19.1 g (70%) of the desired title product. mp 52.5°-53.5°C.

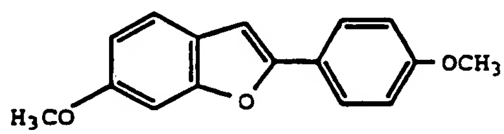
Analysis for $C_{16}H_{16}O_4$:

Theory: C, 68.08; H, 5.71; N, 2.84.

Found: C, 67.86; H, 5.51; N, 2.88.

Preparation 2a

Synthesis of 2-methoxyphenyl-6-methoxybenzofuran.



The cyclization of the product of Preparation 1a was performed essentially as described in C. Goldenberg, et al., Chimie Therapeutique, 398-411 (1973). In a 500 ml 3-neck round bottom flask polyphosphoric acid (30 g) was added to 200 ml of xylene. The mixture was then heated to about 120°C To this heated mixture was then added 2-(3-methoxyphenoxy)-1-(4-methoxyphenyl)ethanone (10 g, 0.037 mole), prepared as described supra, and the temperature was raised to about 170°C, and maintained at that temperature for about eight hours. The reaction mixture was then cooled and water was added.

The dark aqueous layer was separated from the yellow organic phase. The organics were washed with waterand by aqueous sodium carbonate, and then dried over anhydrous magensium sulfate. The solvents were removed in vacuo, resulting in a yellow-orange solid. The product was recrystallized from a minimum of hot acetone, followed by the addition of ethanol and water. The residual acetone was

removed by boiling. Cooling to room temperature yielded white crystals (2.09 g, 22% yield). mp 158°C.

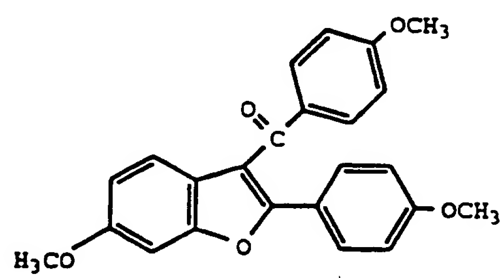
Analysis for $C_{16}H_{14}O_3$:

Theory: C, 75.58; H, 5.55; O, 18.88.

Found: C, 75.33; H, 5.67; O, 18.62.

Preparation 3a

Synthesis of 2-(4-methoxyphenyl)-3-(4-methoxybenzoyl)-6-methoxybenzofuran



In a 250 ml 3-neck round bottom flask were added 2-hydroxy-4-methoxybenzaldehyde (10 g, 65.7 mmol), 1-(4-methoxyphenyl)-2-(4-methoxyphenyl)ethanone (16 g, 62.6 mmol), ethyl acetate (100 ml) and ethanol (25 ml). The reaction mixture was then warmed to about 45°C until all the starting materials were dissolved. Hydrogen chloride gas was then bubbled in for about 30 minutes, resulting in the formation of a bright red coloration. The reaction was then allowed to stand at room temperature for about two hours at which time the solvents were removed in vacuo to leave a bright red oil.

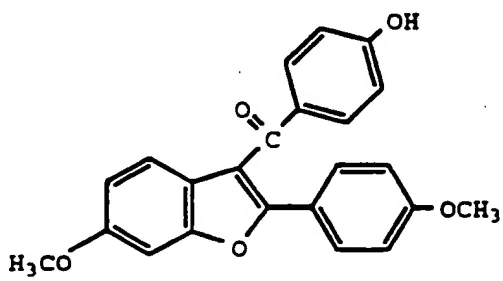
The red oil was dissolved in 180 ml of methanol and 30 ml of 20% sulfuric acid was added with stirring and cooling. Hydrogen peroxide (30 ml) was added dropwise and the mixture was allowed to stir for about 30 minutes. A saturated sodium chloride solution (500 ml) and ethyl acetate (300 ml) were added to the reaction mixture and the organic fraction was removed. The organic layer was washed with a saturated sodium chloride solution, dried, and the solvents were removed in vacuo to provide 25 g of a reddish brown oil

which was further purified by chromatography to yield the title product (1.25 g) as a yellow oil. mp 106-109°C.
Analysis for $C_{24}H_{20}O_5$:

Theory: C, 74.21; H, 5.19; O, 20.60.
Found: C, 74.07; H, 5.22; O, 20.38.

Preparation 4a

Synthesis of 2-(4-methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxybenzofuran



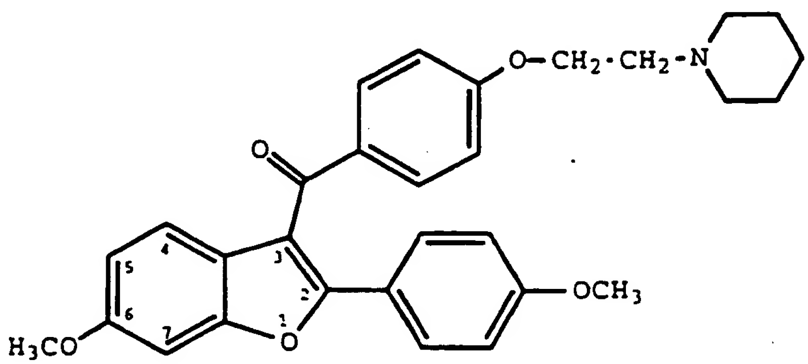
In a three-neck round bottom flask under a nitrogen atmosphere and cooled in an ice bath, ethanethiol (0.95 ml, 1.288 mmol) was dissolved in 10 ml of anhydrous N,N-dimethylformamide. To this solution was added n-butyllithium (0.60 ml of a 1.6 M in hexane solution, 0.966 mmole) followed by the addition of 2-(4-methoxyphenyl)-3-(4-methoxybenzoyl)-6-methoxybenzofuran (250 mg, 0.644 mmole), prepared as described in Preparation 3, supra. The reaction mixture was then heated to 80°C and allowed to remain at that tempeature for about 16 hours.

The reaction mixture was then poured into 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was then washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed in vacuo. The desired product was further purified by column chromatography. The product was then crystallized from methanol yielding 130 mg (81%) of the desired product. mp 148-149°C.
Analysis for $C_{23}H_{18}O_5$:

Theory: C, 73.79; H, 4.85; O, 21.37.
Found: C, 73.68; H, 5.12; O, 21.17.

Example 18

Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran



Method A: Acylation of Benzofuran

4-[2-(Piperidin-1-yl)ethoxy]benzoyl chloride (0.562 g, 1.96 mmol) was added to ethylene chloride (20 ml), followed by the addition of 2-methoxyphenyl-6-methoxybenzofuran (0.500 g, 1.96 mmol), prepared as described in Preparation 2a, supra. This mixture was stirred at room temperature as aluminum trichloride (1.96 g, 14.7 mmol) was added. This reaction mixture was then stirred overnight.

The reaction mixture was then poured over ice, and extracted with warm chloroform (3 x 50 ml). The chloroform was removed by evaporation. Sodium carbonate, water and ethyl acetate were then added and the organic layer was removed, dried over magnesium sulfate, and the solvents were removed in vacuo to provide a yellow oil. The desired product was further purified by chromatography of the yellow oil to yield the desired title product.
NMR, IR, MS.

Analysis for $C_{30}H_{31}NO_5$:

Theory: C, 74.21; H, 6.44; N, 2.88; O, 16.47.

Found: C, 74.11; H, 6.71; N, 2.75; O, 16.57.

Method B: Alkylation of 2-(4-methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxybenzofuran.

In 100 ml of anhydrous N,N-dimethylformamide in a 500 ml round bottom flask were added 2-(4-methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxybenzofuran (10.50 g, 28 mmol), prepared as described in Preparation 4a, supra, and potassium carbonate (6.20 g, 34 mmol). This mixture was heated to 100°C and then 2-(piperidin-1-yl)ethyl chloride (6.20 g, 34 mmol) was added gradually. The reaction mixture was kept at 100°C for about one hour.

The N,N-dimethylformamide was evaporated and the residue was dissolved in ethyl acetate and water. The ethyl acetate layer was removed and the aqueous layer was washed with more ethyl acetate. The organic fractions were combined, dried over magnesium sulfate, and the solvents were removed in vacuo, yielding 13.3 g of a yellow oil which crystallized upon standing. The product was recrystallized from methanol cooled to -30°C prior to filtration, yielding 11.4 g (84%) of the desired product as pale yellow crystals. mp 87-89°C.

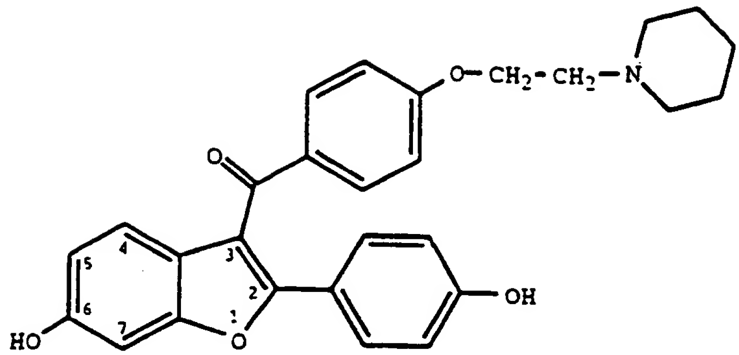
Analysis for $C_{30}H_{31}NO_5$:

Theory: C, 74.21; H, 6.44; N, 2.88; O, 16.47.

Found: C, 74.31; H, 6.34; N, 2.63; O, 16.47.

Example 19

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran



The title product was prepared by the demethylation of 2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran, the product of Example 1a, supra. In a 250 ml three-neck round bottom flask were combined ethylene chloride (50 ml) and aluminum trichloride (9.60 g, 72 mmol) and ethanethiol (6.39 g, 103 mmol) to create a pale yellow liquid. To this liquid was then added the product of Example 1a (5.00 g, 10.3 mmol) in a gradual fashion. A red oil precipitated and the mixture was stirred for about 20 minutes. After cooling the reaction mixture in an ice bath 100 ml of tetrahydrofuran was added and the mixture was allowed to stir until all of the oil had gone into solution.

The reaction mixture was then poured over ice (200 ml) and water (500 ml) and concentrated hydrochloric acid (10 ml) were added. The oil which precipitated was separated from the liquid by decantation. The liquid was extracted with chloroform (warm, 2 x 300 ml). The oil was dissolved by mixing with ethyl acetate, chloroform, sodium bicarbonate, and a small amount of sodium hydroxide. The chloroform extract and the dissolved oil were transferred to separatory funnel and washed with sodium bicarbonate. The organic phase was then dried over magnesium sulfate and the solvents were removed by evaporation to yield a yellow foam, which was further purified by high performance liquid chromatography. NMR, IR, MS.

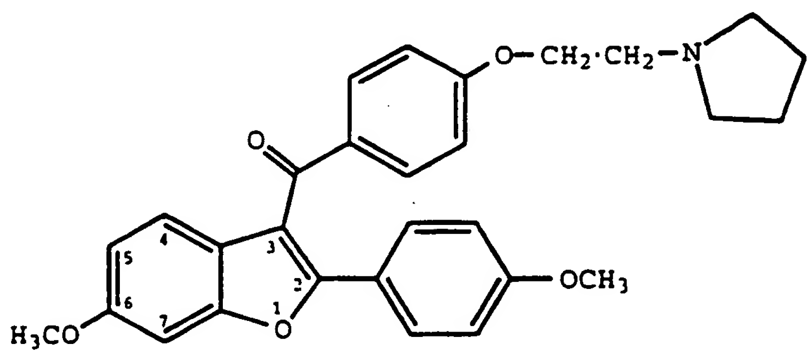
Analysis for $C_{28}H_{27}NO_5$:

Theory: C, 73.51; H, 5.95; N, 3.06.

Found: C, 70.45; H, 6.34; N, 4.02.

Example 20

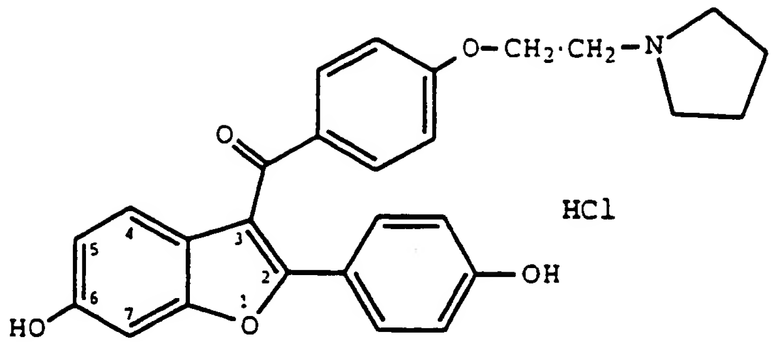
Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran hydrochloride



The title compound is prepared essentially as described in the process for preparing the compound of Example 18 except that 4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl chloride is employed in the synthesis of Method A in place of 4-[2-(piperidin-1-yl)ethoxy]benzoyl chloride or 2-(pyrrolidin-1-yl)ethyl chloride is employed in the synthesis of Method B in place of the 2-(piperidin-1-yl)ethyl chloride.

Example 21

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran hydrochloride



The title compound is prepared essentially as described in Example 19 except that 2-(4-methoxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran is used as the starting material instead of 2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran. NMR, IR, MS.

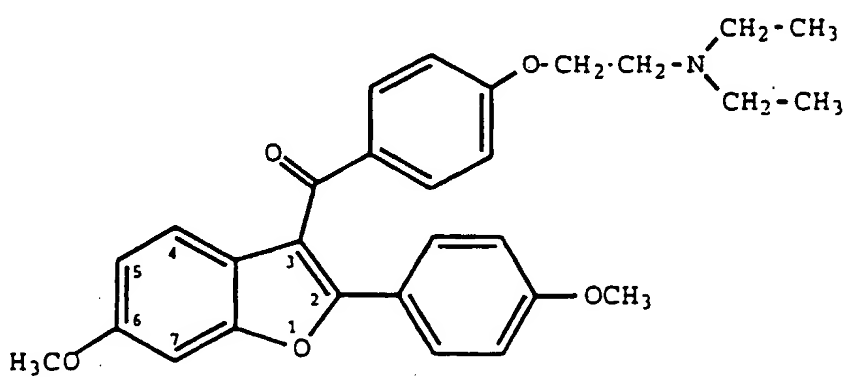
Analysis for $C_{27}H_{26}NO_5Cl$:

Theory: C, 67.57; H, 5.46; N, 2.92.

Found: C, 67.84; H, 5.56; N, 2.87.

Example 22

Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(diethylamino)ethoxy]benzoyl]-6-methoxybenzofuran



The title compound was prepared by reacting the compound of Preparation 4a supra, 2-(4-methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxybenzofuran (10 g, 26.7 mmol) which

is dissolved in 200 ml of N,N-dimethylformamide with an equimolar amount of 2-(N,N-diethylamino)ethyl chloride (6.4 g, 32 mmol) and potassium carbonate (11.06 g, 80.2 mmol). The mixture was heated to 100°C and was maintained at that temperature for about two hours. The reaction mixture was then cooled to room temperature and maintained at this temperature overnight while stirring.

The solvents were then removed by evaporation and the residue was extracted from water with ethyl acetate and washed twice with a saturated sodium chloride solution. The organic phase was dried over sodium sufate and the solvents were removed in vacuo. The material was crystallized from hexane and recrystallized in methanol.

NMR, IR, MS.

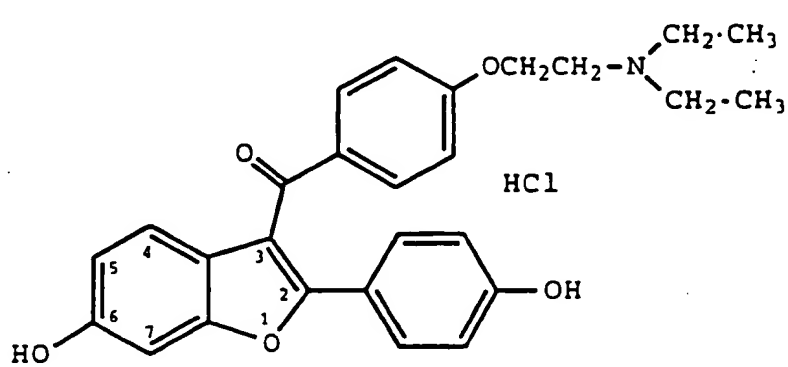
Analysis for $C_{29}H_{31}NO_5$:

Theory: C, 73.55; H, 6.60; N, 2.96.

Found: C, 73.29; H, 6.50; N, 2.84.

Example 23

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(diethylamino)ethoxy]benzoyl]-6-hydroxybenzofuran hydrochloride



The title compound was prepared essentially as described in Example 19, supra, except that the compound of Example 5, 2-(4-methoxyphenyl)-3-[4-[2-

(diethylamino)ethoxy]benzoyl]-6-methoxybenzofuran, was used as the starting material to be demethylated.

NMR, IR, MS.

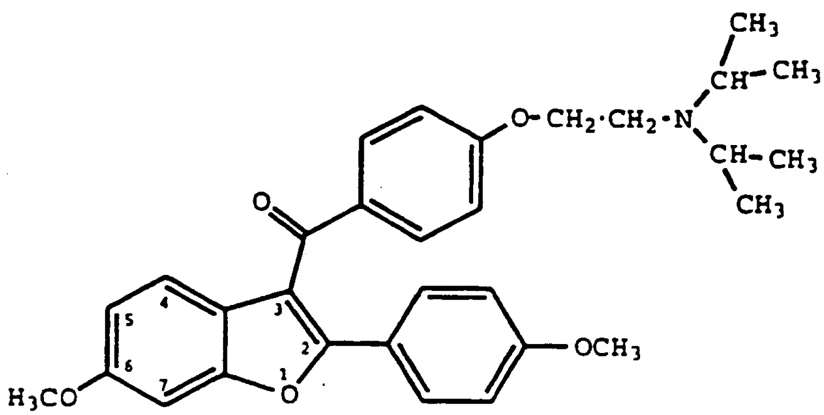
Analysis for $C_{27}H_{28}NO_5Cl$:

Theory: C, 67.29; H, 5.86; N, 2.91.

Found: C, 67.54; H, 5.64; N, 2.92.

Example 24

Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(diisopropylamino)ethoxy]benzoyl]-6-methoxybenzofuran



The title compound was prepared by reacting the compound of Preparation 4a supra, 2-(4-methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxybenzofuran (10 g, 26.7 mmol) which is dissolved in 200 ml of N,N-dimethylformamide with 2-(N,N-diisopropylamino)ethyl chloride (6.4 g, 32 mmol) and potassium carbonate (11.06g, 80.2 mmol). The mixture was heated to 100°C and was maintained at that temperature for about two hours. The reaction mixture was then cooled to room temperature and maintained at this temperature overnight while stirring.

The solvents were then removed by evaporation and the residue was extracted from water with ethyl acetate and washed twice with a saturated sodium chloride solution. The organic phase was dried over sodium sufate and the solvents

were removed in vacuo. The material was crystallized from hexane and recrystallized in methanol.

NMR, IR, MS.

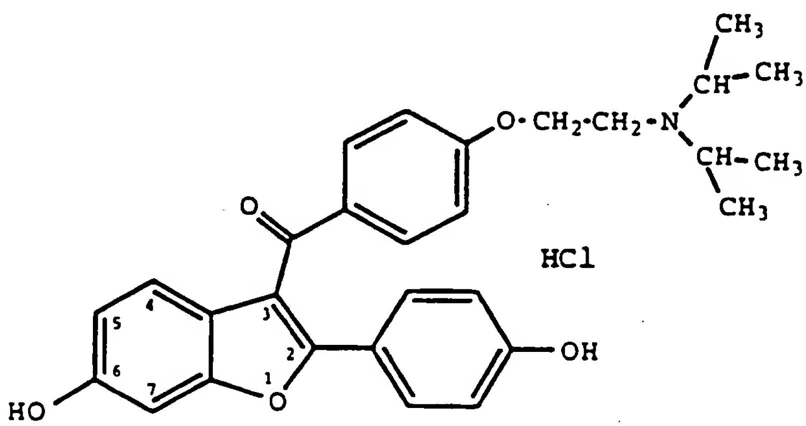
Analysis for $C_{33}H_{39}NO_5$:

Theory: C, 74.83; H, 7.42; N, 2.64.

Found: C, 74.68; H, 7.14; N, 2.76.

Example 25

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(diisopropylamino)ethoxy]benzoyl]-6-hydroxybenzofuran hydrochloride



The title compound was prepared essentially as described in Example 19, supra, except that the compound of Example 24, 2-(4-methoxyphenyl)-3-[4-[2-(diisopropylamino)ethoxy]benzoyl]-6-methoxybenzofuran, was used as the starting material to be demethylated.

NMR, IR, MS.

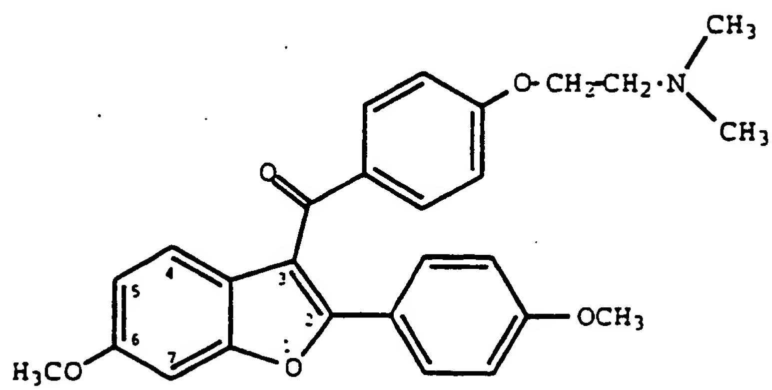
Analysis for $C_{29}H_{32}NO_5Cl$:

Theory: C, 68.29; H, 6.32; N, 2.75.

Found: C, 68.53; H, 6.49; N, 2.74.

Example 26

Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(dimethylamino)ethoxy]benzoyl]-6-methoxybenzofuran



The title compound was prepared essentially as described in Example 24, supra, except that 2-(N,N-dimethylamino)ethyl chloride was reacted with 2-(4-methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxybenzofuran instead of the 2-(N,N-diisopropylamino)ethyl chloride employed in that example.

NMR, IR, MS.

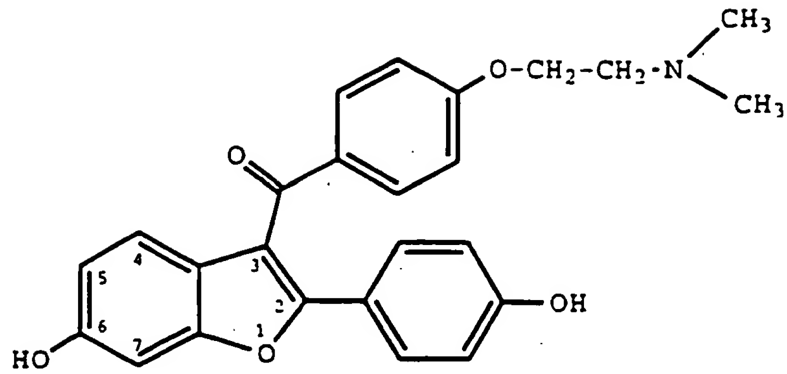
Analysis for $C_{27}H_{27}NO_5$:

Theory: C, 72.79; H, 6.11; N, 3.14.

Found: C, 72.51; H, 6.27; N, 3.10.

Example 27

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(dimethylamino)ethoxy]benzoyl]-6-hydroxybenzofuran



The title compound was prepared essentially as described in Example 19, supra, except that the compound of Example 26, 2-(4-methoxyphenyl)-3-[4-[2-(dimethylamino)ethoxy]benzoyl]-6-methoxybenzofuran, was used as the starting material to be demethylated.

NMR, IR, MS.

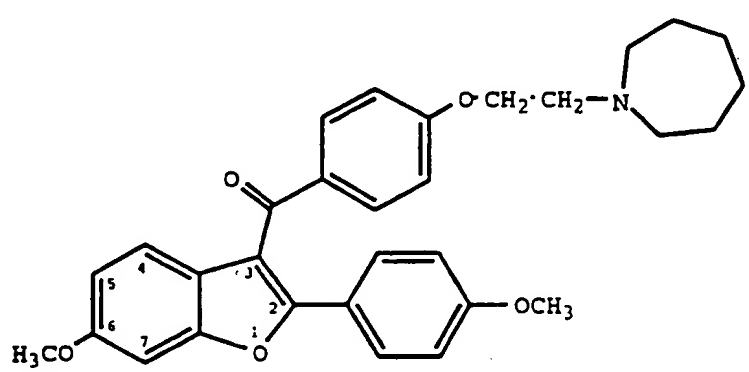
Analysis for $C_{25}H_{23}NO_5$:

Theory: C, 71.93; H, 5.55; N, 3.36.

Found: C, 70.69; H, 5.51; N, 3.16.

Example 28

Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran



The title compound was prepared essentially as described in Example 24, supra, except that 2-(hexamethyleneimin-1-yl)ethyl chloride was reacted with 2-(4-

methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxybenzofuran instead of the 2-(N,N-diisopropylamino)ethyl chloride employed in that example.

NMR, IR, MS.

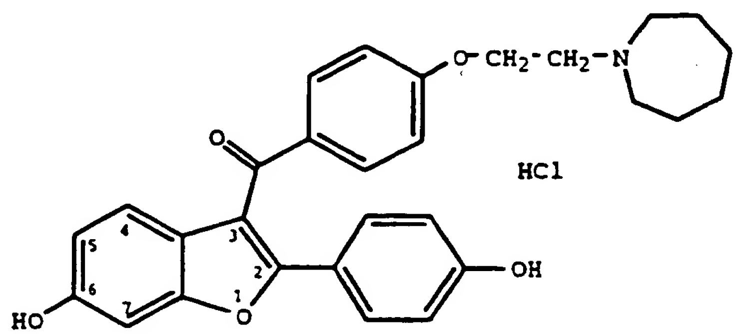
Analysis for $C_{31}H_{33}NO_5$:

Theory: C, 74.53; H, 6.66; N, 2.80.

Found: C, 74.69; H, 6.70; N, 2.75.

Example 29

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran hydrochloride



The title compound was prepared essentially as described in Example 19, supra, except that the compound of Example 28, 2-(4-methoxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran, was used as the starting material to be demethylated.

NMR, IR, MS

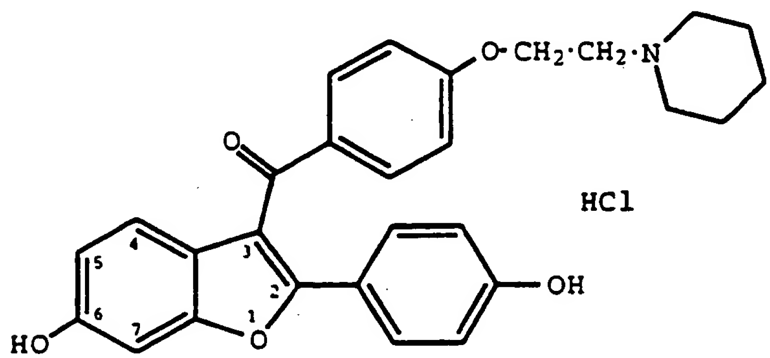
Analysis for $C_{29}H_{30}ClNO_5$:

Theory: C, 68.57; H, 5.95; N, 2.76.

Found: C, 67.28; H, 6.13; N, 2.66.

Example 30

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran hydrochloride



The title compound was prepared by dissolving the compound of Example 19, 2-(4-hydroxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran, (3.1 g, 6.8 mmol) in 15 ml of methanol and treating with an excess of 3% hydrochloric acid in methanol. The volume was then reduced by boiling to 15 ml. Warm water (20 ml) was then added and the reaction mixture was further warmed to clarify. The reaction mixture was then filtered, followed by gradual cooling to 0°C, at which temperature the mixture was maintained for about one hour. The crystals, which had precipitated, were collected by filtration and washed with cold water. The pale yellow crystals were dried overnight, resulting in 2.82 g (84%) of the desired title product. mp 213-215°C.

NMR, IR, MS.

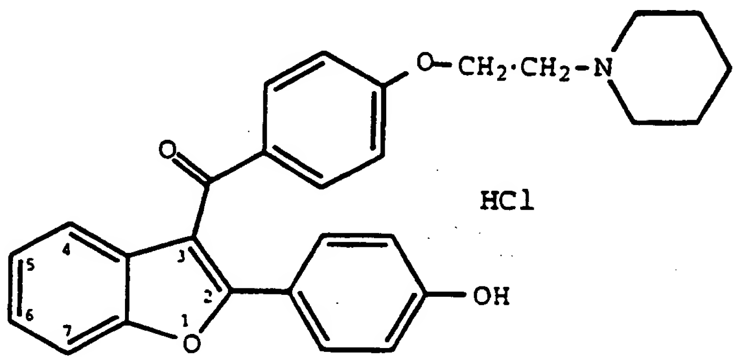
Analysis for $C_{28}H_{28}NO_5Cl$:

Theory: C, 68.08; H, 5.71; N, 2.84; O, 16.19.

Found: C, 67.86; H, 5.51; N, 2.88; O, 15.93.

Example 31

Synthesis of 2-(4-hydroxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzofuran hydrochloride



The 2-(4-hydroxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzofuran was prepared essentially as described in Example 19, except that phenol was used as a starting material in the synthesis described in Preparation 2a instead of 3-methoxy phenol. The hydrochloride salt of this substituted benzofuran was prepared essentially as described in Example 30, supra.

NMR, IR, MS.

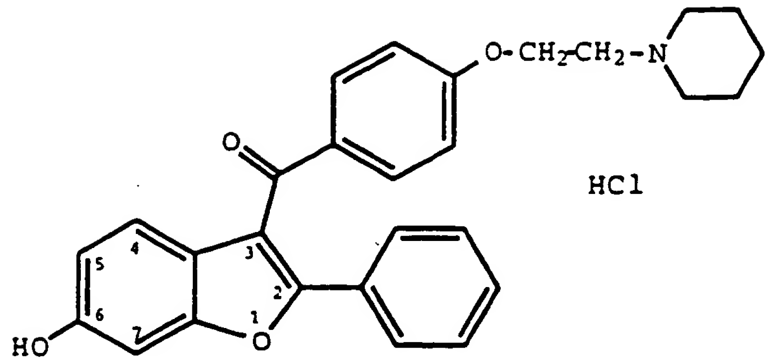
Analysis for $C_{28}H_{28}NO_4Cl$:

Theory: C, 70.36; H, 5.91; N, 2.93.

Found: C, 70.46; H, 5.84; N, 2.84.

Example 32

Synthesis of 2-phenyl-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran hydrochloride



The 2-phenyl-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran was prepared essentially as described in Example 19, except that phenacylbromide (also known as α-bromoacetophenone) was used as a starting material in the synthesis described in Preparation 1a instead of 4-methoxyphenacylbromide. The hydrochloride salt of this substituted benzofuran was prepared essentially as described in Example 30, _supra_.

NMR, IR, MS.

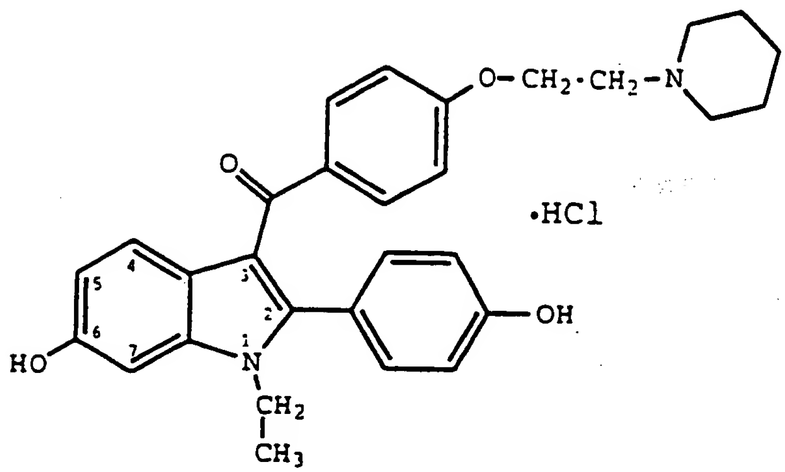
Analysis for $C_{28}H_{28}NO_4Cl$:

Theory: C, 70.36; H, 5.90; N, 2.93.

Found: C, 70.39; H, 6.01; N, 2.91.

Example 33

Synthesis of 1-ethyl-2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxyindole hydrochloride salt



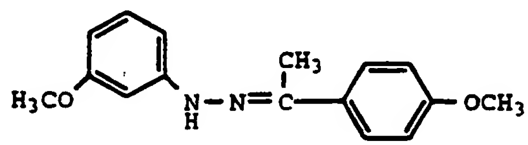
To 814 milliliters of concentrated hydrochloric acid in a 3 liter, 3-neck round bottom flask which had been cooled to 0°C was added 3-methoxyaniline (99.26 g, 0.806 mole). Sodium nitrate (55.61 g, 0.806 mole), dissolved in 249 milliliters of water, was added dropwise to the 3-methoxyaniline solution at such a rate that the reaction temperature never exceeded 0°C. This mixture was then stirred for about 90 minutes.

Stannous chloride (545.57 g, 2.418 mol), dissolved in 497 milliliters of concentrated hydrochloric acid, was added dropwise to the reaction mixture at such a rate that the reaction temperature never exceeded 5°C. This mixture was then stirred for about two hours after the addition of the stannous chloride was completed, resulting in the formation of a thick, beige, chalky emulsion. The solid was removed by filtration, stored overnight in one liter of water and then basified with a 25% solution of sodium hydroxide. This aqueous solution was extracted with diethyl ether (3 x 1 liter) and then dried over sodium sulfate. The solvents were removed in vacuo, resulting in a brown oil of 3-methoxyphenylhydrazine (76.3 g, 69% yield).

The 3-methoxyphenylhydrazine (76.3 g, 0.552 mole) prepared supra, was dissolved in 400 milliliters of ethanol. To this mixture was added p-methoxyacetophenone (82.80 g, 0.552 mole) followed by the addition of about 6 drops of

hydrochloric acid. This mixture was then stirred for about seven hours under a nitrogen atmosphere, followed by storage at 4°C for about 3 days.

The white solid was then removed from the suspension by filtration under vacuum and then dried _in vacuo_, resulting in 135.2 grams (91% yield) of [(3-methoxyphenyl)hydrazono]-1-methyl-4-methoxybenzylidene of the following formula as a pale gray solid.



Zinc chloride (66.5 g, 0.49 mole) was added to a 3-neck round bottom flask under a nitrogen atmosphere. The flask and its contents were then heated to 200°C at which time the hydrazone (26.4 g, 0.098 mole) prepared _supra_ was added. The mixture was stirred for about 17 minutes, resulting in the formation of a brown tar and the evolution of some gas. The brown tar was then poured into two liters of 0.075 N hydrochloric acid and this mixture was stirred for about 48 hours, resulting in the formation of a yellow solid.

The solids were removed by filtration and were then recrystallized from methanol. The solids were again removed by filtration and the solvents were removed _in vacuo_ to yield the desired 2-(4-methoxyphenyl)-6-methoxyindole (5.50 g, 22% yield) as a white crystalline product.

The 2-(4-methoxyphenyl)-6-methoxyindole (2.0 g, 8 mmol) was dissolved in 40 milliliters of N,N-dimethylformamide. This solution was added dropwise to a solution of sodium hydride (0.48 g, 12 mmol) in ten milliliters of N,N-dimethylformamide. This reaction mixture was then stirred at room temperature for 1 hour at which time a solution of ethyl iodide (1.9 g, 12 mmol) in N,N-dimethylformamide (10 ml) was added dropwise over five

minutes. This mixture was then stirred at room temperature for about two hours.

The reaction was quenched by the addition of methanol. The volume of the solvents was reduced by vacuum, leaving a brown oil. This oil was diluted with chloroform, washed with 5 N sodium hydroxide (3 x 75 ml), followed by washing with water (2 x 200 ml). The organic layer was dried over sodium sulfate and the solvents were removed *in vacuo* leaving 2.3 g of the desired intermediate 1-ethyl-2-(4-methoxyphenyl)-6-methoxyindole as white crystals.

The preceding intermediate was acylated at the 3-position by first placing N,N-dimethyl-4-methoxybenzamide (1.43 g, 8 mmol), in a 100 ml flask cooled to 0°C. To this was then added phosphorous oxychloride (6.1 g, 40 mmol) dropwise at such a rate that the reaction temperature never exceeded 20°C. The reaction mixture was allowed to warm to room temperature and was stirred for about 30 minutes. The reaction mixture was then cooled to 0°C and the 1-ethyl-2-(4-methoxyphenyl)-6-methoxyindole (1.5 g, 5.33 mmol) prepared *supra*, was added and the reaction mixture was then heated to 75°C and maintained at this temperature for about three hours.

After this incubation, the reaction mixture was poured over ice and diluted with water. The layers were separated and the organic phase was washed with water (150 ml). The organic layer was dried over sodium sulfate and the oslvents were removed *in vacuo* to yield a dark brown/black oil. This oil was taken up in 50 milliliters of methanol and cooled to 0°C. This solution was then basified by the dropwise addition of 2N sodium hydroxide (50 ml). The mixture was then heated to reflux for about 5 minutes, then cooled overnight at 4°C.

The precipitate was then removed by filtration and recrystallized from methanol, resulting in 2.21 grams (86% yield) of the intermediate 1-ethyl-2-(4-methoxyphenyl)-3-(4-methoxybenzoyl)-6-methoxyindole as a yellow precipitate.

The above intermediate (2.1 g, 5.05 mmol) was then admixed with sodium thioethoxide (0.85 g, 10.11 mmol) in N,N-dimethylformamide (12 ml). The reaction mixture was then heated to 85°C and maintained at this temperature for about six hours. The desired intermediate 1-ethyl-2-(4-methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxyindole was then recrystallized from ethyl acetate.

This intermediate (1.5 g, 3.74 mmol) was then reacted with 2-(piperidin-1-yl)ethyl chloride hydrochloride (1.38 g, 7.5 mmol) in N,N-dimethylformamide (60 ml) in the presence of cesium carbonate (3.26 g, 10 mmol). This admixture was heated to 80°C and maintained at this temperature for about two hours.

The precipitate was collected by filtration and then taken up in chloroform, and washed with 2 N sodium hydroxide (3 x 125 ml) and water (3 x 100 ml). The organic fraction was then dried over sodium sulfate and the solvents were removed _in vacuo_ to yield 2.05 grams (95% yield) of 1-ethyl-2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxyindole as a gray foam.

This intermediate (1.0 g, 1.82 mmol) was dissolved in dichloromethane (10 ml) and cooled to 0°C. To this mixture was then added the Lewis acid aluminum chloride (1.2 g, 9 mmol) and the reaction mixture was then stirred for five minutes. Ethanol (3 ml) were then added and the reaction mixture was stirred on ice for about 15 minutes. The temperature of the reaction mixture was slowly raised to reflux and maintained at reflux for about 1.5 hours.

The reaction mixture was then cooled to 0°C and this temperature was maintained as tetrahydrofuran (5 ml) was added. To this mixture was then added 20% hydrochloric acid in water (5 ml) and the reaction mixture was cooled back to 0°C at which time five milliliters of water was then added, resulting in the formation of a yellow gum. This suspension was then placed at -40°C and kept at this temperature for about 48 hours, after which time a grayish material was removed from the mixture by filtration. Thin layer

chromatography confirmed this precipitate as the desired title product.

NMR, MS.

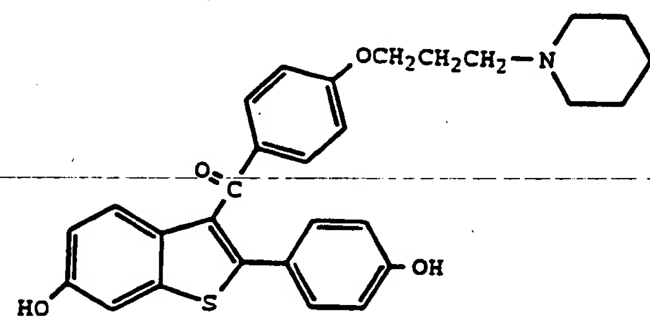
Analysis for $C_{30}H_{33}ClN_2O_4$:

Theory: C, 69.15; H, 6.38; N, 5.38.

Found: C, 69.09; H, 6.43; N, 5.53.

Example 34

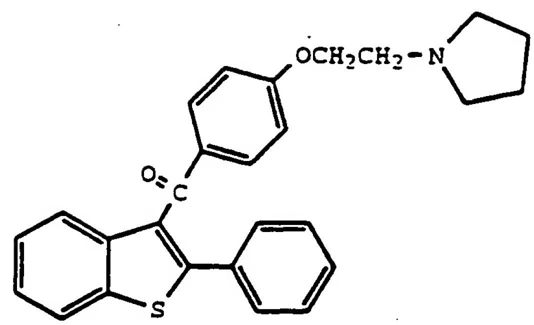
Synthesis of 2-(4-hydroxyphenyl)-3-[4-[3-(piperidin-1-yl)propoxy]benzoyl]-6-hydroxybenzo[b]thiophene hydrochloride



The title compound was prepared essentially as described in U.S. Patent 4,380,635, which is herein incorporated by reference with the exception that 4-[3-(piperidin-1-yl)propoxy]benzoyl chloride was used to acylate the substituted benzo[b]thiophene rather than the 4-[2-(piperidin-1-yl)ethoxy]benzoyl chloride employed therein.

Example 35

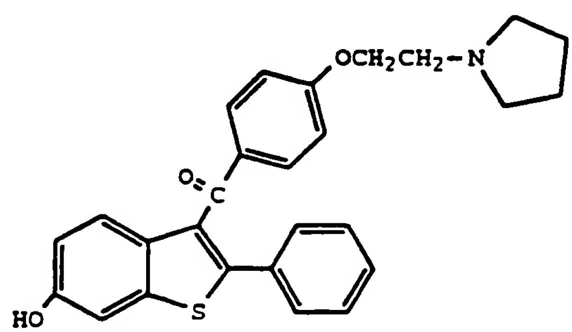
Synthesis of 2-phenyl-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 36

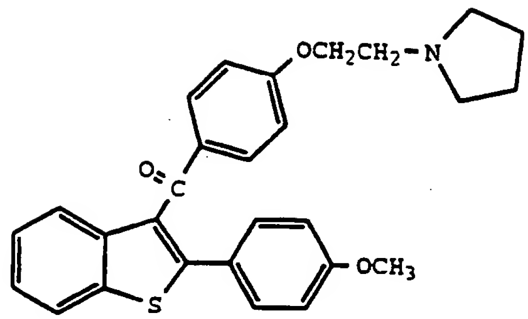
Synthesis of 2-phenyl-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-6-methoxybenzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 37

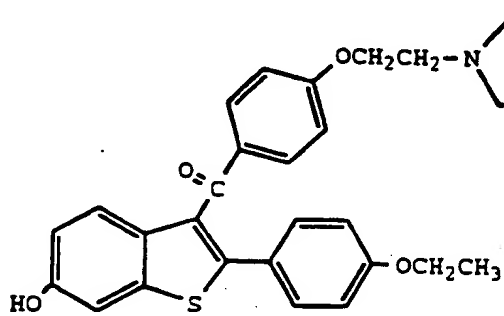
Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 38

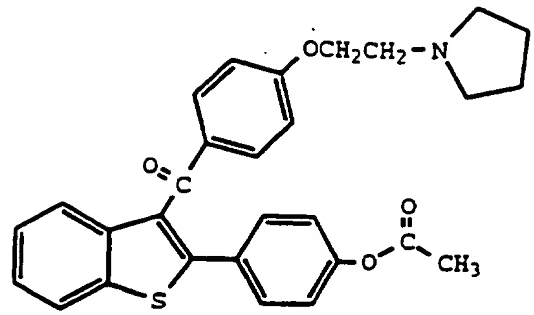
Synthesis of 2-(4-ethoxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-6-methoxybenzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 39

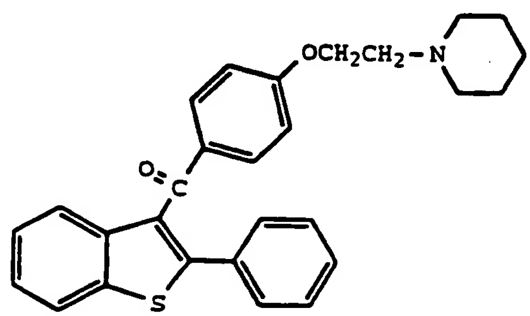
Synthesis of 2-(4-acetoxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 40

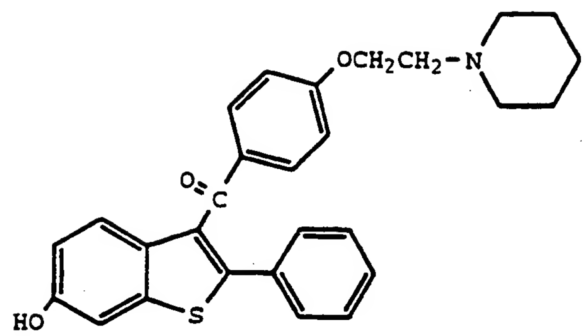
Synthesis of 2-phenyl-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 41

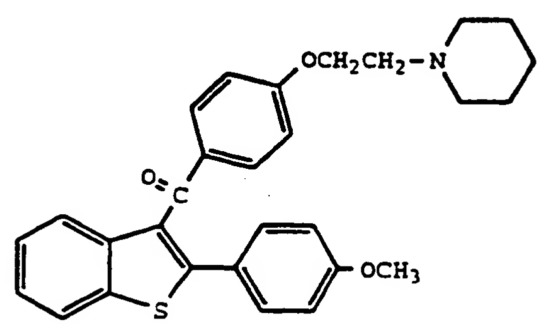
Synthesis of 2-phenyl-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxybenzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 42

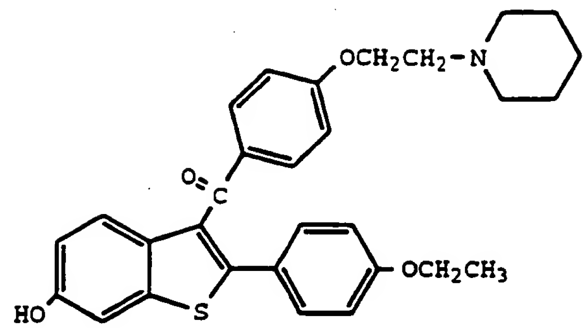
Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 43

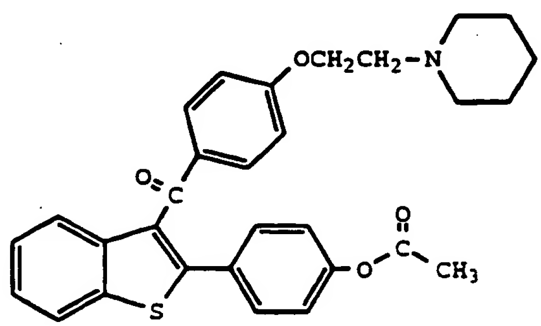
Synthesis of 2-(4-ethoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxybenzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 44

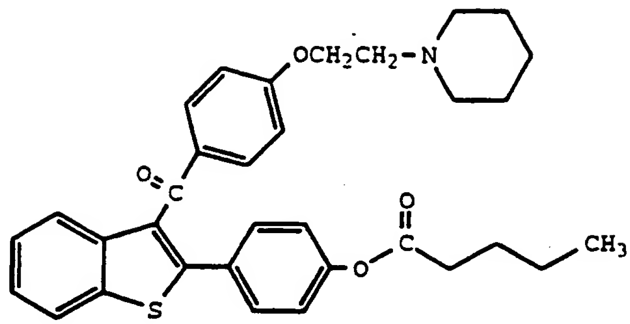
Synthesis of 2-(4-acetoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 45

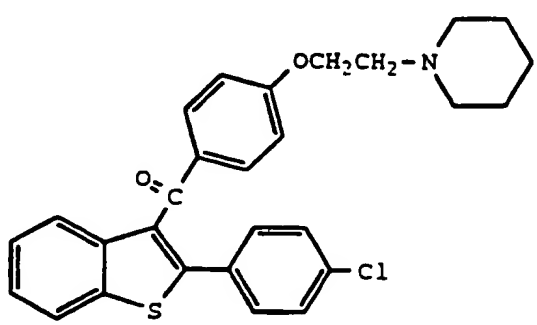
Synthesis of 2-(4-pentanoylphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound, also known as 2-(4-valerylphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate, was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 46

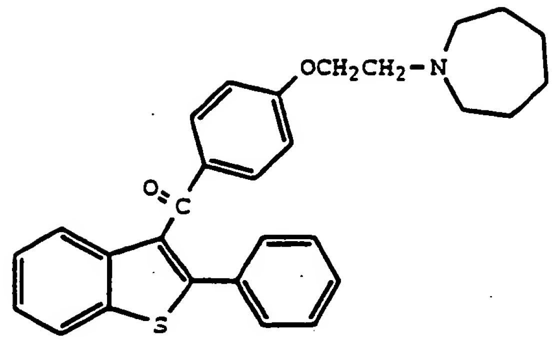
Synthesis of 2-(4-chlorophenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 47

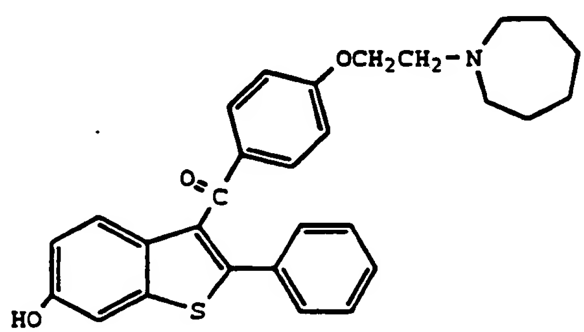
Synthesis of 2-phenyl-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]benzo[b]thiophene



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 48

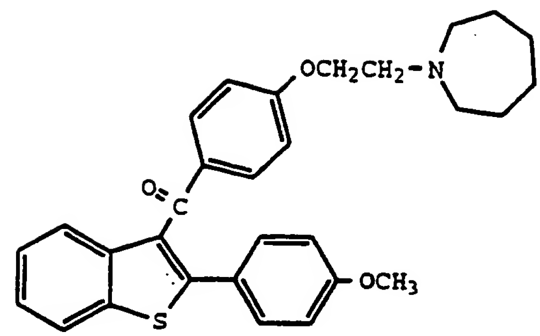
Synthesis of 2-phenyl-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-methoxybenzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 49

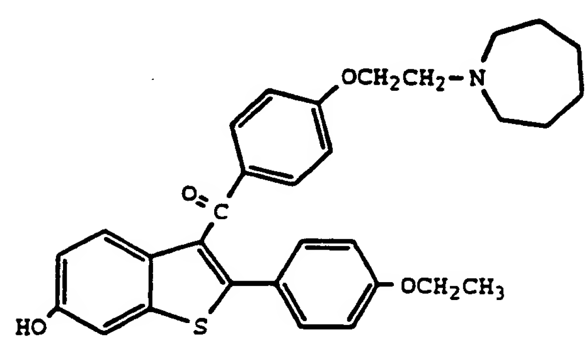
Synthesis of 2-(4-methoxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 50

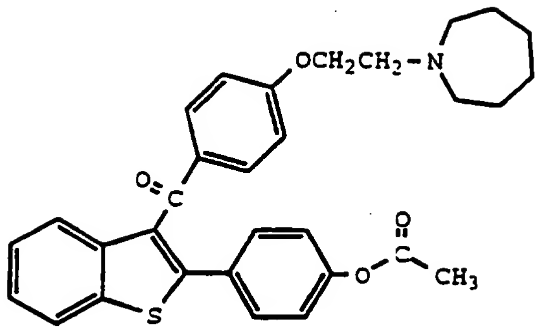
Synthesis of 2-(4-ethoxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-methoxybenzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 51

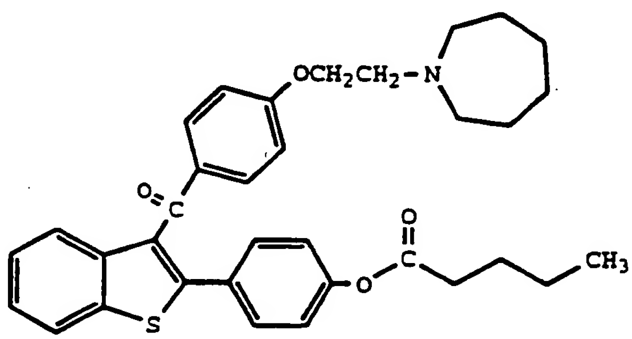
Synthesis of 2-(4-acetoxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 52

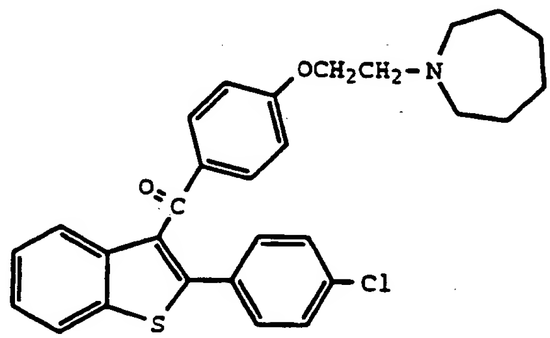
Synthesis of 2-(4-pentanoylphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound, also known as 2-(4-valerylphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate, was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 53

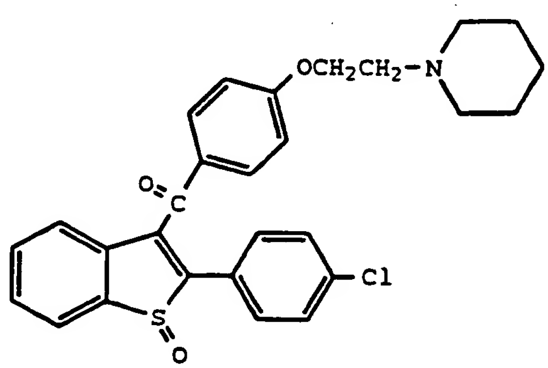
Synthesis of 2-(4-chlorophenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]benzo[b]thiophene citrate



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Example 54

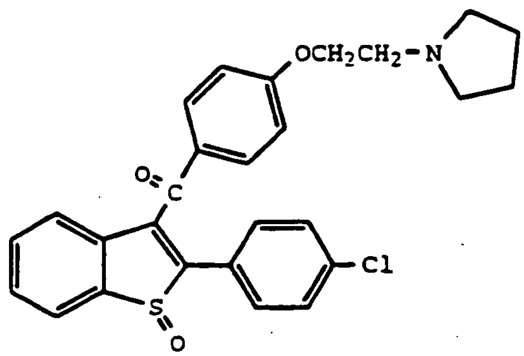
Synthesis of 2-(4-chlorophenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene-1-oxide



The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

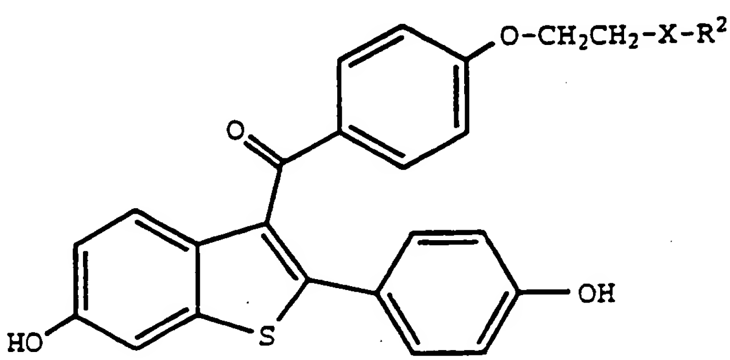
Example 55

Synthesis of 2-(4-chlorophenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene-1-oxide



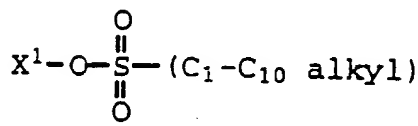
The title compound was prepared as described in U.S. Patent 4,133,814, which is herein incorporated by reference.

Those compounds employed in the methods of the instant invention in which R or R^1 are $-OSO_2-(C_1-C_{10}$ alkyl) or $-O\overset{\overset{O}{\|}}{C}\underset{H}{N}-R^3$ were made essentially as described in European Patent Application 617,030, published September 28, 1994. Those compounds employed in the methods of the instant invention wherein at least one of R^1 and R is $-OSO_2-(C_1-C_{10}$ alkyl) were generally prepared by reacting a compound of Formula II



II

with an alkyl sulfonyl of Formula IIa



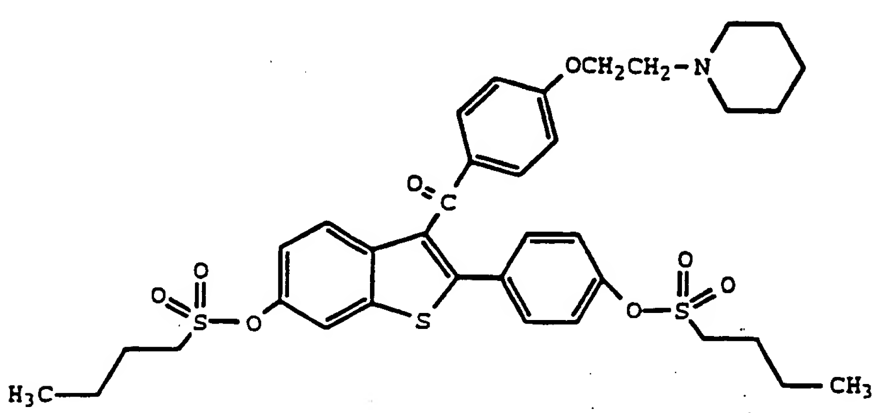
IIa

where X^1 is a leaving group, preferably a chloro or bromo group. This reaction is usually performed in a basic environment in the presence of a coupling catalyst such as 4-dimethylaminopyridine (DMAP). Most preferred solvents include the lower alkyl amines, especially triethylamine. While this thioester formation reaction may be performed at equal molar ratios of the two reactants, it is usually preferred to employ a 2-3 molar excess of the alkyl sulfonyl compound so as to complete the reaction.

The following examples will illustrate preparation of these compounds of this invention but are not intended to limit it in any way..

<u>Example 56</u>

Preparation of [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone



In dry tetrahydrofuran (250 ml) [6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxyphenyl]-methanone, hydrochloride (5.1 g, 10 mmol) was suspended and 7.1 g (70 mmol) of triethylamine was added. The reaction mixture was cooled to 0°C in an ice bath and 10 mg of 4-dimethylaminopyridine (DMAP) was added, followed by the slow addition of n-butylsulfonyl chloride (4.7 g, 30 mmol). The reaction mixture was placed under a nitrogen atmosphere and allowed to warm slowly to room temperature and continued for 72 hours. The reaction mixture was filtered and evaporated to an oil. The oily residue was dissolved in chloroform and chromatographed on a silica gel column and eluted with a linear gradient of chloroform to chloroform-methanol (19:1; V:V). The desired fractions were combined and evaporated to dryness to afford 5.60 g of the title compound as a tan amorphous powder.

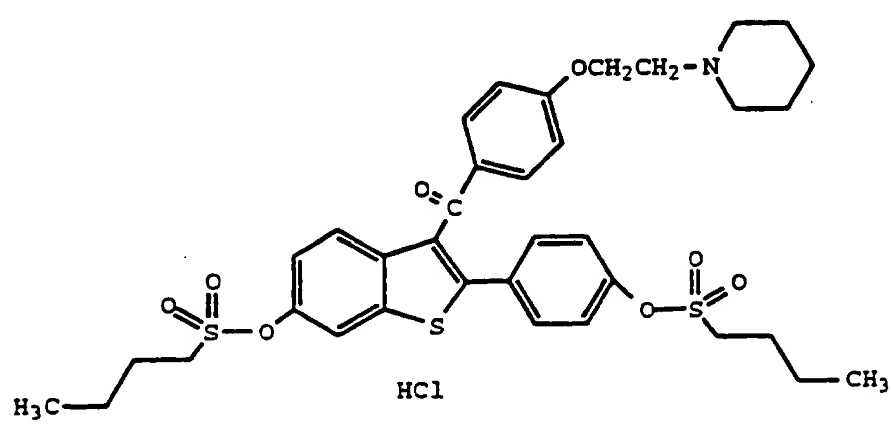
$C_{36}H_{43}NO_8S_3$

MS (FD) m/e=714 (M+1)

NMR was consistent with the proposed structure.

Example 57

Preparation of [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone, Hydrochloride



The commpound of Example 1, [6-(n-Butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]-benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone (5.4 g) was dissolved in ethyl acetate (EtOAc) and a solution of ether, saturated with hydrochloric acid, was added until no more precipitate was formed. The liquid was decanted off and the solid was triturated with ether. The title compound was crystallized from hot ethyl acetate to afford 3.74 g, as a white powder.

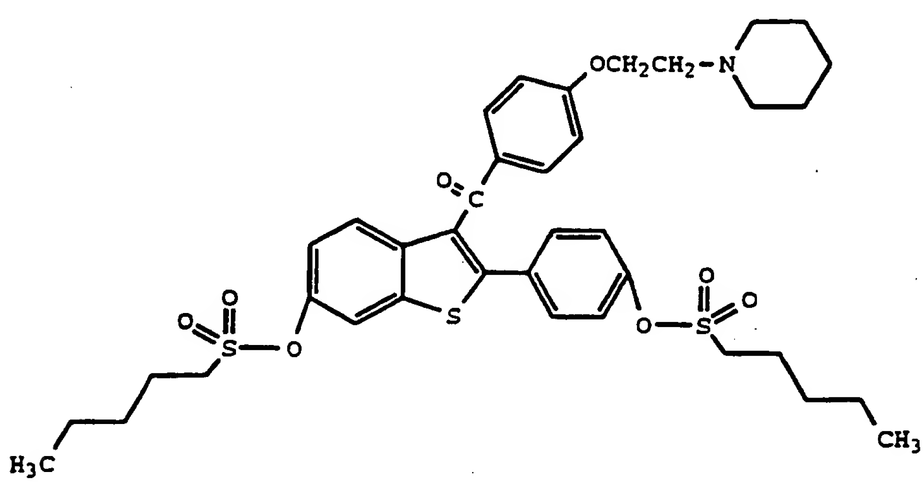
$C_{36}H_{43}NO_8S_3$-HCl

Elemental Analysis:	C	H	N
Calculated:	57.7	5.88	1.87
Found:	57.75	5.93	1.93

NMR was consistent with the proposed structure.

Example 58

Preparation of [6-(n-pentylsulfonoyl)-2-[4-(n-pentylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone



In dry tetrahydrofuran (100 ml) of [6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl-]methanone, hydrochloride (3 g, 5.9

mmol) was suspended and 10 mg of DMAP was added followed by 3 g (30 mmol) of triethylamine. The reaction mixture was stirred at room temperature and under a nitrogen blanket for about 20 minutes. n-Pentyl sulfonyl chloride (2.5 g, 14.7 mmol) was dissolved in 25 ml of tetrahydrofuran and slowly added to the stirring reaction mixture. The reaction was allowed to proceed at room temperature and under nitrogen for eighteen hours. The reaction mixture was filtered and the volatiles were removed <u>in vacuo</u>. The resulting material was dissolved in a small amount of chloroform and chromatographed (HPLC) on a silica gel column eluted with a linear gradient starting with chloroform and ending with chloroform-methanol (19:1 v/v). The desired fractions were determined by thin layer chromatography, combined and evaporated down to afford 3.82 g of the title compound as thick oil.

$C_{38}H_{47}NO_8S_3$

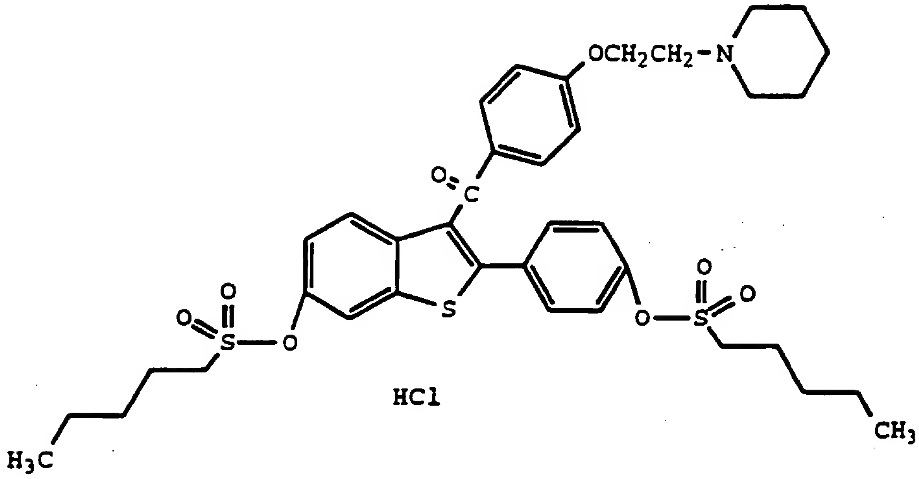
NMR: consistent with the proposed structure

MS: (FD) m/e=743 (M+2)

Elemental Analysis:	C	H	N
Calculated:	61.51	6.39	1.89
Found:	57.63	6.44	1.50

<u>Example 59</u>

Preparation of [6-(n-pentylsulfonoyl)-2-[4-(n-pentylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone, Hydrochloride



[6-(n-Pentylsulfonoyl)-2-[4-(n-pentylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone (3.7 g) was dissolved in 25 ml of ethyl acetate and a solution of hydrochloric acid saturated diethyl ether was added. A precipitate formed and the liquid decanted off. The gummy solid was triturated with diethyl ether and dried _in vacuo_ at room temperature to afford 2.12 g of the title compound as a white amorphous and hygroscopic solid.

$C_{38}H_{47}NO_8S_3$ HCl

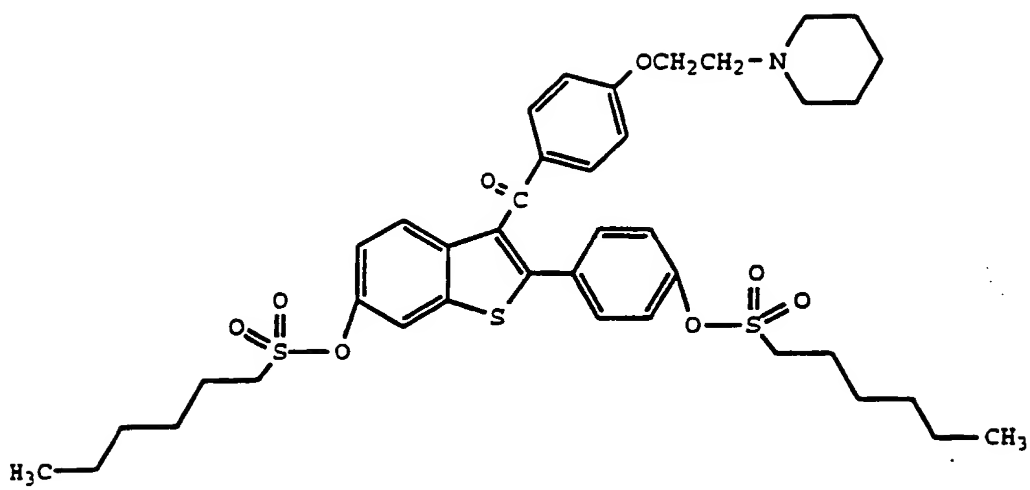
NMR: consistent with the proposed structure

Elemental Analysis:

	C	H	N
Calculated:	58.63	6.22	1.80
Found:	57.35	6.45	1.38

Example 60

Preparation of [6-(n-hexylsulfonoyl)-2-[4-(n-hexylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone



In dry tetrahydrofuran (250 ml) 3 g (5.9 mmol) of [6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-methanone hydrochloride was suspended and 10 mg of DMAP was added. Triethylamine (4 g, 40 mmol) was then added and the reaction mixture was stirred for 20 minutes at room temperature under a nitrogen blanket. n-Hexylsulfonyl chloride (3.6 g, 19.6 mmol) in 25 ml of tetrahydrofuran was slowly added to the reaction mixture. The reaction was allowed to proceed at room temperature and under nitrogen for 3 days. The reaction mixture was evaporated down <u>in vacuo</u> and resuspended in ethyl acetate and washed with water. The organic layer was dried by filtering it through anhydrous sodium sulfate and evaporated to a yellow oil. The oil was dissolved in chloroform and chromatographed (HPLC) on a silica gel column and eluted with a linear gradient starting with chloroform and ending with chloroform-methanol (19:1 v/v). The desired fractions were determined by thin layer chromatography, combined and evaporated down to afford 3.14 g of the title compound as a thick oil.

$C_{40}H_{51}NO_8S_3$

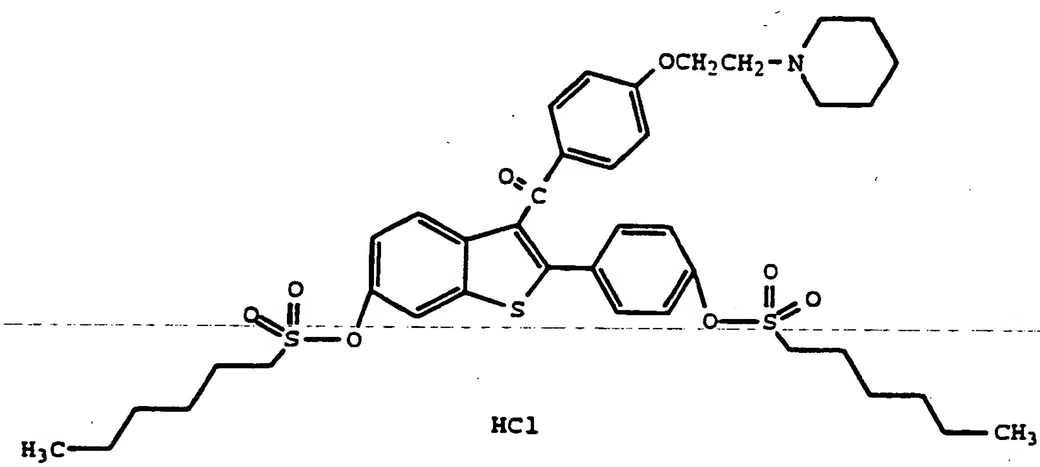
NMR: consistent with the proposed structure

MS: (FD) m/e=771 (M+1)

Elemental Analysis:	C	H	N
Calculated:	62.39	6.68	1.82
Found:	62.33	6.62	2.03

Example 61

Preparation of [6-(n-Hexylsulfonoyl)-2-[4-(n-hexylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone, Hydrochloride



[6-(n-Hexylsulfonoyl)-2-[4-(n-hexylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone (3 g) was dissolved in 20 ml of ethyl acetate and hydrochloric acid-saturated diethyl ether was added. No precipitate formed. The reaction mixture was evaporated to a thick oil and was triturated several times with diethyl ether and dried in vacuo at room temperature to afford 1.64 g of the title compound as a white amorphous and hygroscopic powder.

NMR: consistent with the proposed structure

Elemental Analysis:	C	H	N
Calculated:	59.67	6.50	1.74
Found:	59.47	6.59	1.77

$C_{40}H_{51}NO_8S_3$-HCl

Example 62

Preparation of [6-(n-Butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone, Citrate

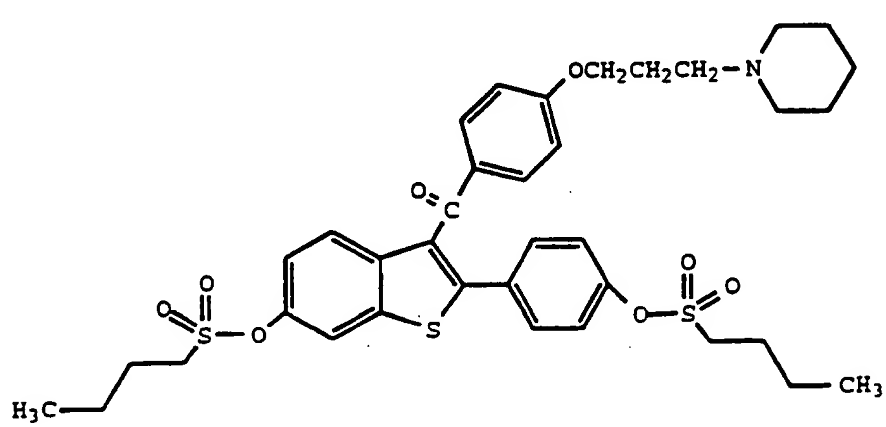
2 g (2.8 mmol) of [6-(n-Butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone was dissolved in 200 ml of acetone and 0.63 g (3 mmol) of citric acid was added. The reaction mixture remained at room temperature and under a nitrogen blanket for eighteen hours. The reaction mixture was evaporated *in vacuo* at 50° C. The reaction mixture was triturated several times with ether and dried at room temperature *in vacuo* to afford 2.35 g of the title compound as a white amorphous and hygroscopic powder.

Elemental Analysis:	C	H	N
Calculated:	55.68	5.67	1.55
Found:	55.39	5.60	1.60

NMR: consistent with the proposed structure

Example 63

Preparation of [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[3-(1-piperidinyl)propoxy]phenyl]methanone



2.5 g (4.77 mmol) of [6-hydroxy-2-[4-hydroxyphenyl]benzo-[b]thien-3-yl][4-[3-(1-piperidinyl)propoxy]-phenyl]methanone hydrochloride was dissolved in 100 ml of tetrahydrofuran, 3.9 g (39 mmol) of triethylamine and 10mg of DMAP were added. The reaction mixture was stirred for 15 minutes at room temperature and under a nitrogen blanket. 4 g (25.5 mmol) of n-butylsulfonyl chloride in 15 ml of tetrahydrofuran was slowly added. The reaction was allowed to proceed for eighteen hours at room temperature and under nitrogen. The reaction was quenched with the addition of 25 ml methanol and volume reduced _in vacuo_. The crude product was chromatographed on a silica gel column, eluted with chloroform-methanol (19:1 v/v). The desired fractions were determined by thin layer chromatography, combined, and evaporated to a tan oil.

Example 64

Preparation of [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[3-(1-piperidinyl)propoxy]-phenyl] methanone, hydrochloride

[6-(n-Butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]-benzo[b]thien-3-yl][4-[3-(1-piperidinyl)propoxy]-phenyl] methanone was dissolved in ethyl acetate-hexane and hydrogen chloride gas was bubbled in. The reaction mixture was evaporated down and chromatographed (HPLC) on a silica gel column eluted with chloroform and then with chloroform-methanol (19:1 v/v). The desired fractions were determined by thin layer chromatography and combined and evaporated down to a tan amorphous powder to afford 2.5 g of the title compound.

NMR: consistent with the proposed structure
MS: (FD) m/e=728 (M-HCl)

Elemental Analysis:	C	H	N
Calculated:	58.14	6.07	1.83
Found:	57.90	6.05	1.82

$C_{37}H_{46}NO_8S_3$-HCl

Example 65

Preparation of [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone.

1.5 g of [6-hydroxy-2-[4-hydroxyphenyl]benzo[b]thien-3-yl][4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]methanone hydrochloride (3 mmol) was suspended in 200 ml of tetrahydrofuran. 1.5 g of triethylamine (15 mmol) and 10 mg of 4-N,N-dimethylaminopyridine were added. The reaction mixture was stirred for several minutes under a nitrogen atmosphere. 1.56 g of n-butylsulfonyl chloride (10 mmol) was dissolved in 50 ml of tetrahydrofuran and slowly added to the reaction mixture over a twenty minute period. The reaction mixture was stirred for eighteen hours at room temperature and under a nitrogen atmosphere. The reaction mixture was evaporated to a gum *in vacuo*. The crude product was suspended in 100 ml of ethyl acetate and washed with sodium bicarbonate solution and subsequently with water. The organic layer was dried by filteration through anhydrous sodium sulfate and evaporated to a yellow oil. The final product was crystallized from hot ethyl acetate-hexane to afford 410 mg of the title compound.

NMR was consistent with the proposed structure
MS: m/e = 700 (M+1) FD

Elemental Analysis:	C	H	N
Calculated:	60.20	5.86	2.01
Found:	59.94	5.94	2.00

MW = 699
$C_{35}H_{41}NO_8S$

Example 66

Preparation of [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)-phenyl]benzo[b]thien-3-yl]-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]methanone hydrochloride;

350 mg of [6-(n-Butylsulfonoyl)-2-[4-Butylsulfonoyl)-phenyl]benzo[b]thien-3-yl]-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]methanone (0.5 mmol) was dissolved in 10 ml of ethyl acetate and a saturated solution of hydrogen chloride in ether was added. No precipitate formed and the reaction mixture was evaporated to a gummy, white solid. The product was triturated with diethyl ether (2x) and filtered and dried *in vacuo* at room temperature to afford 220 mg of the title compound.

NMR: consistent with the proposed structure

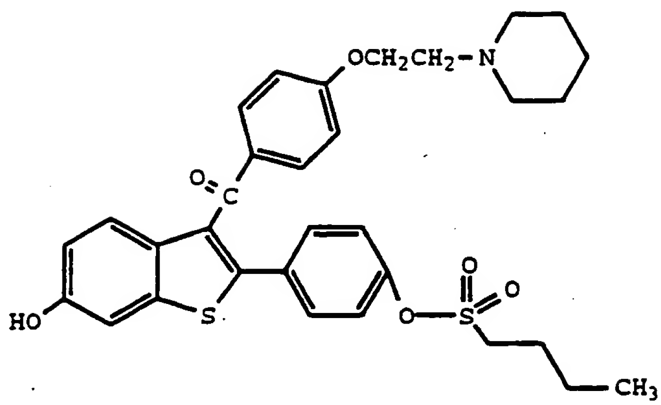
Elemental Analysis:	C	H	N
Calculated	57.09	5.75	1.90;
Found:	57.27	5.91	1.86

MW = 736.37

$C_{35}H_{41}NO_8S_3$ - HCl

Example 67

Preparation of [6-hydroxy-2-[4-(n-butylsulfonoyl)-phenyl]benzo[b]-thien-3-yl]-[4-[2-(1-piperidinyl)-ethoxy]phenyl]methanone.



20 g of [6-hydroxy-2-[4-hydroxyphenyl]benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (Raloxifene) hydrochloride (0.04 mol) was suspended in 250 ml of tetrahydrofuran. Ten grams of triethylamine (0.1 mol) and 10 mg of 4-N,N-dimethylaminopyridine were added. The reaction mixture was stirred for several minutes under nitrogen. 6.25 g of n-butylsulfonylchloride (0.04 mol) was dissolved in 25 ml of tetrahydrofuran and slowly added to the reaction mixture over a period of twenty minutes. The reaction was allowed to continue for 5 days at room temperature and under nitrogen atmosphere. The reaction mixture was evaporated to a gum and suspended in ethyl acetate. The ethyl acetate mixture was washed successively with water, dilute sodium bicarbonate, and water. The ethyl acetate solution was dried by filteration through anhydrous sodium sulfate and evaporated to an amorphous solid.

The resulting solid was dissolved in 50 ml of methylene chloride and chromatographed (HPLC) on a silica gel column eluted with a linear gradient of chloroform to chloroform-methanol (19:1)(v/v). Four fractions were determined by thin layer chromatography and evaporated *in vacuo* to amorphous solids:

Fraction A: [6-(n-Butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl] methanone, 5.43 g

Fraction B:	[6-hydroxy-2-[4-(n-butylsulfonoyl)-phenyl]benzo[b]-thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, 2.19 g, Rf=0.50, silica gel, $CHCl_3$-MeOH (19:1)v/v
Fraction C:	[6-(n-butylsulfonoyl)-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, 3.60 g Rf=0.41, silica gel, $CHCl_3$-MeOH (19:1)v/v
Fraction D:	Raloxifene, 3.94 g

All of Fraction B was dissolved in hot ethyl acetate and hexane was added and the title compound crystallized out to afford 1.89 g of the title compound.

NMR: consistent with proposed structure
MS: m/e=594(M+1) FD

Elemental Analysis:	C	H	N
Calculated:	64.80	5.90	2.36
Found:	64.85	6.07	2.49

$C_{32}H_{35}NO_6S_2$

Example 68

Preparation of [6-hydroxy-2-[4-(n-butylsulfonoyl)-phenyl]benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride.

1.7 g of [6-hydroxy-2-[4-(n-butylsulfonoyl)-phenyl]benzo[b]-thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (2.86 mmol) was dissolved in ethyl acetate and a saturated solution of hydrogen chloride-diethyl ether was added. A thick white precipitate formed. The liquid was decanted off. The remaining solid was triturated with diethyl ether (2x) and dried to afford 1.57 g of the title compound as a white amorphous powder.

NMR: consistent with the proposed structure.

Elemental Analysis:	C	H	N
Calculated:	60.99	5.76	2.22;
Found:	61.17	5.88	2.27

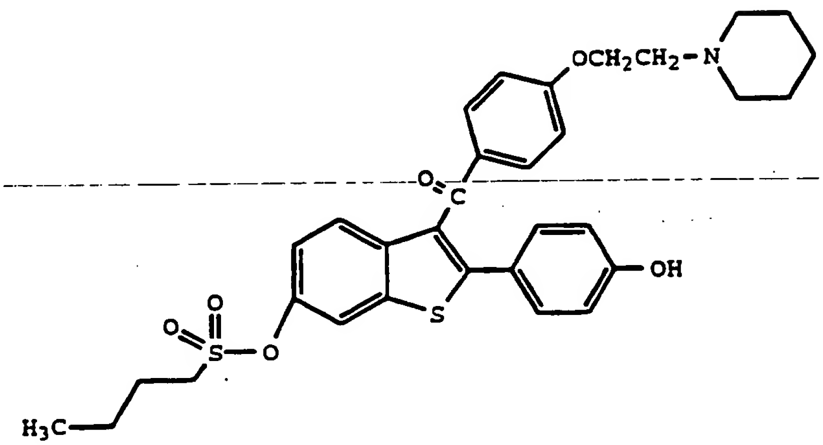
MW = 630.23

$C_{32}H_{35}NO_6S_2$ - HCl

MS: m/e = 594 (M-HCl)F.D.

Example 69

Preparation of [6-n-butylsulfonoyl-2-[4-hydroxyphenyl]benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone.



All of fraction C from Example 67 was dissolved in 50 ml of hot ethyl acetate and hexane. No crystallization occurred The solvents were evaporated *in vacuo* to afford 3.17 g of the title compound as oily, white solid.

NMR: consistent with the proposed structure.

MS: m/e = 594 (M+1) FD

Elemental Analysis:	C	H	N
Calculated:	64.84	5.90	2.36.
Found:	64.37	5.87	2.28.

MW = 593

$C_{32}H_{35}NO_6S$

Example 70

Preparation of [6-n-butylsulfonoyl-2-[4-hydroxyphenyl]benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride.

3 g of [6-n-butylsulfonoyl-2-[4-hydroxyphenyl]-benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone was dissolved in 50 ml of ethyl acetate and a solution of diethyl ether saturated with hydrogen chloride was added. A thick white precipitate formed and the liquid was decanted off. The solid was triturated (2x) with diethyl ether and dried. This afforded 2.51 g of the title compound as a white amorphous powder.

NMR: consistent with the proposed structure.

Elemental Analysis:	C	H	N
Calculated:	60.99	5.76	2.22;
Found:	60.71	5.84	2.21

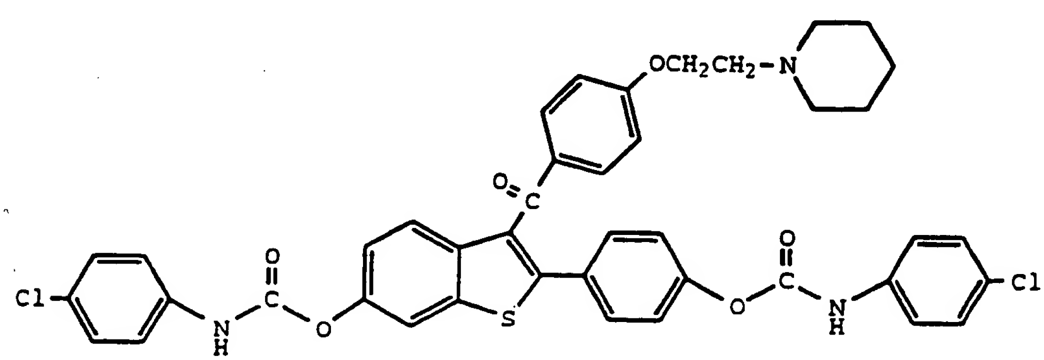
MW = 630.23

$C_{32}H_{35}NO_6S_2$ - HCl

MS: m/e = 594 (M-HCl) F.D.

Example 71

Preparation of [6-[N-(4-chlorophenyl)carbamoyl]-2-[4-[N-(4-chlorophenyl)carbamoyl]phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl] methanone.



5.56 g (10.7 mmol) of [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was dissolved in 200 ml of dry tetrahydrofuran and 5.45 g (35.2 mmol) of 4-chlorophenyl isocynate was added. The reaction mixture was stirred at room temperature under an atmosphere of nitrogen. After 18 hours, the solvent was removed by evaporation in vacuo, and redissolved in chloroform. The chloroform solution was cooled to -20°C for 24 hours and the precipitate formed was filtered off. The remaining solution was chromatographed (Waters Prep 500, HPLC) on a silica gel column, eluted with a linear gradient of chloroform ending with chloroform-methanol (19:1)(v/v). The desired fractions were determined by thin layer chromatography, combined and evaporated to dryness to afford 4.01 g of the title compound as a tan amorphous powder.

$C_{42}C_{35}Cl_2N_3O_6S$

Elemental Analysis:	C	H	N
Calculated:	64.64	4.48	5.38
Found:	65.69	4.81	4.83

MS (FD) m/e=779,781

Example 72

Preparation of [6-[N-(4-chlorophenyl)carbamoyl]-2-[4-[N-(4-chlorophenyl)carbamoyl]phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl] methanone hydrochloride.

4.01 g of [6-[N-(4-Chlorophenyl)carbamoyl]-2-[4-[N-(4-chlorophenyl)carbamoyl]phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone was dissolved in 200 ml of ether and a small amount of tetrahydrofuran added to affect solution. A solution of ether, which had been saturated with hydrogen chloride, was added until no further precipitate formed. The reaction mixture was evaporated to

dryness and triturated with ether several times. An attempt was made to crystalize the salt from hot ethyl acetate and absolute EtOH, which did work. Evaporation of the solvent, afforded 2.58 g of the title compound as a tan amorphous powder.

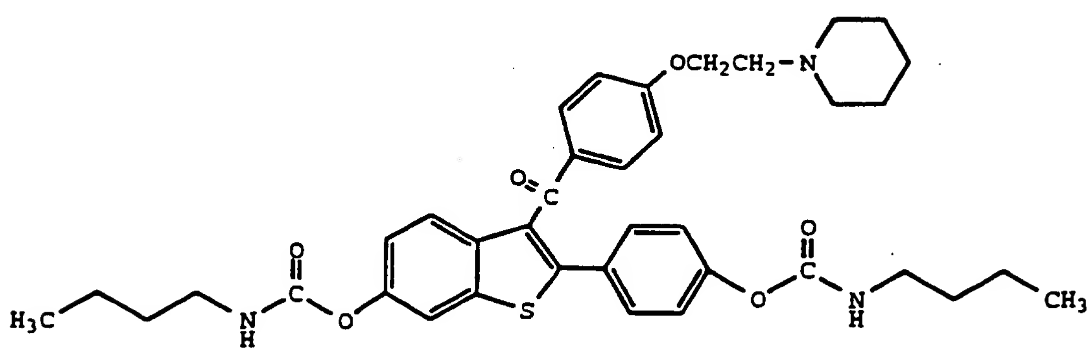
$C_{42}H_{35}Cl_2N_3O_6S$-HCl

Elemental Analysis:	C	H	N
Calculated:	61.73	4.44	5.14
Found:	57.43	4.29	4.19

NMR: Consistent with the proposed structure and contains an indeterminate amount of solvent.

Example 73

Preparation of [6-(N-(n-butyl)carbamoyl]-2-[4-(N-(n-butyl)carbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl] methanone.



4.47 g (9 mmol) of [6-hydroxy-2-(4-hydroxyphenyl)benzo-[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was dissolved in 250 ml of tetrahydrofuran and 4 g (40 mmol) of n-butylisocyanate was added. The reaction mixture, at room temperature and under nitrogen, was allowed to react for 72 hours. The reaction mixture had evaporated by the end of this time and the residue was dissolved in a minimal amount

of chloroform. This solution was chromatographed (HPLC) on a silica gel column, eluted with a linear gradient of chloroform to chloroform-methanol (19:1) to afford 4.87 g of the title compound as a tan amorphous powder.

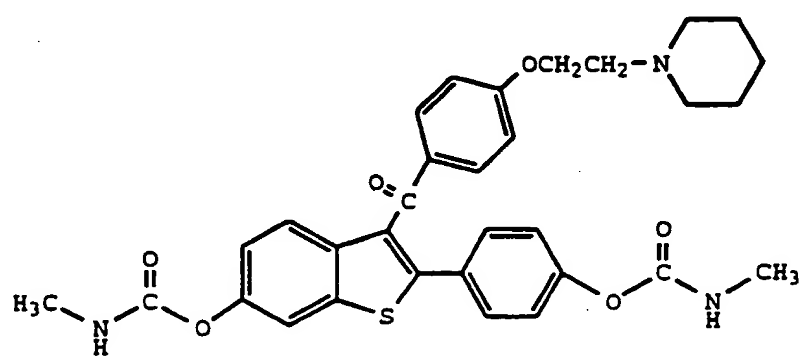
Elemental Analysis:	C	H	N
Calculated:	67.73	6.75	6.52
Found:	66.43	6.67	6.24

MS (FD) m/e=672 (M+1)

NMR was consistent with the proposed structure.

Example 74

Preparation of [6-(N-methylcarbamoyl)-2-[4-(N-methylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone.



A suspension of 3 g (5.9 mmol) of [6-hydroxy-2(4-hydroxyphenyl)]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride in 250 ml of anhydrous tetrahydrofuran was prepared. To this suspension was added 2 g (10 mmol) of triethylamine and the reaction mixture was stirred at room temperature for approximately 15 minutes under a nitrogen atmosphere. To the stirring mixture was added 5.8 g (20 mmol) of methylisocyanate. The reaction was allowed to continue for 36 hours. The reaction mixture was filtered and evapoated to dryness <u>in vacuo</u>. The residue was dissolved in 30 ml of

chloroform and chromatographed (HPLC) on a silica gel column, eluted with a linear gradient of solvent of chloroform to chloroform-methanol (19:1). The fractions were analyzed by thin layer chromatography and the desired fractions were combined and evaporated to dryness in vacuo to afford 2.2 g of the title compound as an amorphous powder.

NMR: Consistent with the proposed structure.
IR: 3465, 2942, 1741 cm-1 ($CHCl_3$)
MS: m/e=588 (M+1) FD
$C_{32}H_{33}N_3O_6S$.

Example 75

Preparation of [6-(N-methylcarbamoyl)-2[4-(N-methylcarbamoyl)-phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone Hydrochloride.

Two grams of the compound of [6-(N-Methylcarbamoyl)-2-[4-(N-methylcarbamoyl)-phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was disolved in 20 ml of ethyl acetate and a solution of hydrochloric acid-ether was added, forming a white precipitate. The reaction mixture was evaporated to dryness in vacuo. The solids were crystallized from acetone-ethyl acetate, filtered and washed with ethyl acetate and dried to afford 1.98 g of the title compound.

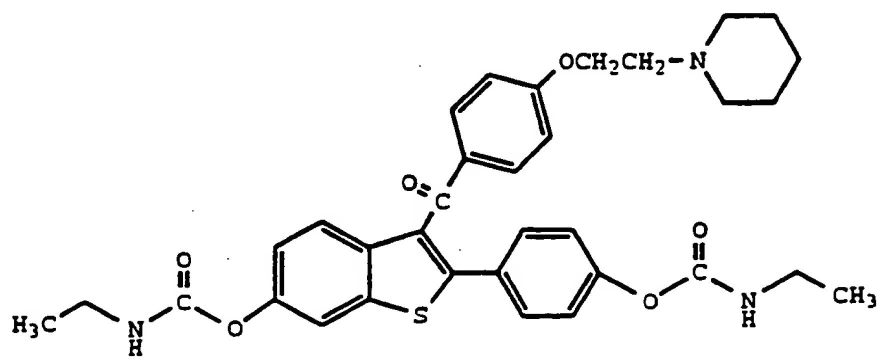
NMR: Consistent with the desired structure.

Elemental Analysis:	C	H	N
Calculated:	61.58	5.49	6.73
Found:	61.25	5.96	5.97.

$C_{32}H_{34}ClN_3O_6S$.

Example 76

Preparation of [6-(N-ethylcarbamoyl)-2-[4-(N-ethylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone.



4 g (7.85 mmol) of [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride was suspended in 250 ml of anhydrous tetrahydrofuran and 3 g (30 mmol) of triethylamine was added. The reaction mixture was stirred at room temperature under nitrogen for 15 minutes. 1.67 g (23.5 mmol) of ethylisocyanate was added. After 24 hours, the reaction was checked by thin layer chromatography, and was not complete. An additional 4.5 g of the isocyanate was added. After 96 hours, the reaction mixture was filtered and chromatographed as in Example 74 to afford 4.23 g of the title compound as a white amorphous powder.

NMR: Consistent with the proposed structure.
MS: m/e=616 (M+1) FD
$C_{34}H_{37}N_3O_6S$.

Example 77

Preparation of [6-(N-ethylcarbamoyl)-2-[4-(N-ethylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride.

This compound was prepared by substantially the same procedures of Example 75, to afford 3.58 g of the title compound.

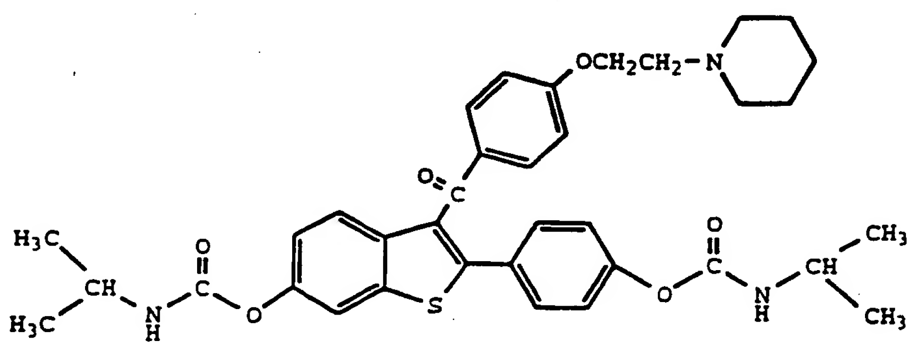
NMR: Consistent with the proposed structure.

Elemental Analysis:	C	H	N
Calculated:	62.61	5.87	6.44;
Found:	62.33	6.16	6.41.

$C_{34}H_{38}ClN_3O_6S$.

Example 78

Preparation of [6-(N-isopropylcarbamoyl)-2[4-(N-isopropylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone.



4 g (7.85 mmol) of [6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-methanone hydrochloride was suspended in 250 ml of anhydrous tetrahydrofuran and 3 g (30 mmol) of triethylamine was added. The reaction mixture was stirred for 15 minutes at room temperature and under nitrogen. 2.77 g (32.6 mmol) of isopropylisocyanate was added. After 24 hours, the reaction was checked by thin layer chromatography for completeness and was not complete. An additional 10.8 g (130.4 mmol) of the isocyanate was added and the reaction was allow to continue for another 96 hours. The desired compound was isolated

substantially according to the procedures described in Example 19 to afford 4.01 g of the title compound as a tan amorphous powder.

NMR: Consistent with the proposed structure.
MS: m/e=644 (M+1) FD
$C_{36}H_{41}N_3O_6S$.

Example 79

Preparation of [6-(N-isopropylcarbamoyl)-2-[4-(N-isopropylcarbamoyl)phenyl]benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride.

This compound was prepared by substantially following the procedures of Example 75 to afford 3.58 g of the title compound as a white crystalline powder.

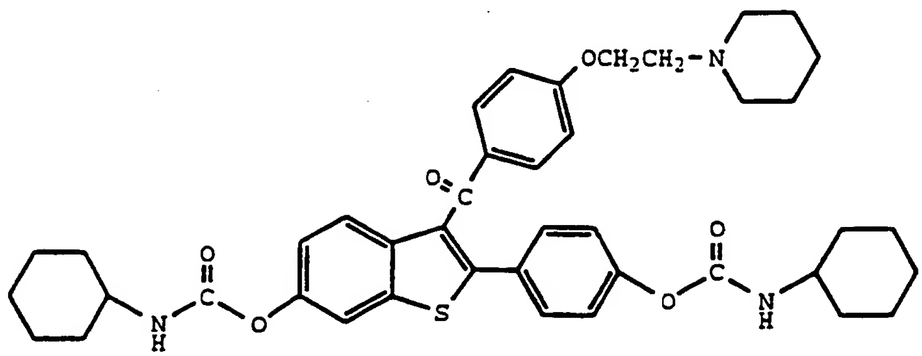
NMR: Consistent with the proposed structure.

Elemental Analysis:	C	H	N
Calculated:	63.56	6.22	6.18
Found:	63.63	6.52	5.95

$C_{36}H_{42}ClN_3O_6S$.

Example 80

Preparation of [6-(N-cyclohexylcarbamoyl)-2[4-(N-cyclohexylcarbamoyl)phenyl]benzo[b]thienyl-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone.



3 g (5.9 mmol) of [6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-methanone hydrochloride was suspended in 250 ml of anhydrous tetrahydrofuran and 2 g (20 mmol)of triethylamine was added. The reaction mixture was stirred for 15 minutes at room temperature under nitrogen. 14.5 g (105 mmol) of cyclohexylisocyanate was added. The reaction was allowed to continue for 48 hours, then an additional 20 mmol of the isocyanate was added. After a further 24 hours, the desired product was isolated substantially according to the procedures of Example 19 to afford 4.07 g of the the title compound as a tan amorphous powder.

NMR: Consistent with the proposed structure.
MS: m/e=724 (M+1) FD
$C_{42}H_{49}N_3O_6S$.

Example 81

Preparation of 6-(N-cyclohexylcarbamoyl)-2-[4-(N-cyclohexylcarbamoyl)phenyl]benzo[b]thienyl-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone Hydrochloride

3.9 g of 6-(N-cyclohexylcarbamoyl)-2[4-(N-cyclohexylcarbamoyl)phenyl]benzo[b]thienyl-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was converted to its hydrochloride salt by substantially the same procedures as described for Example 75 and crystallized from hot ethyl

acetate. This afforded 3 g of the title compound as a white powder.

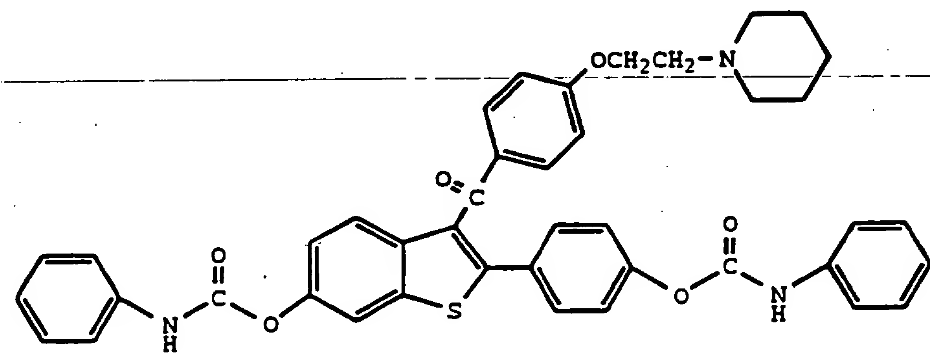
NMR: Consistent with the proposed structure.

Elemental Analysis:	C	H	N
Calculated:	66.34	6.63	5.53
Found:	66.32	6.92	5.62

$C_{42}H_{50}ClN_3O_6S$.

Example 82

Preparation of [6-(N-phenylcarbamoyl)-2-[4-(N-phenylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone.



3 g (5.9 mmol) of [6-hydroxy-[2-(4-hydroxyphenyl)benzo [b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride was suspended in 250 ml of anhydrous tetrahydrofuran and 2 g (20 mmol) of triethylamine was added. The reaction mixture was stirred for 15 minutes at room temperature under nitrogen. 15 ml of phenylisocyanate was added and the reaction was allow to continue for 96 hours. An additional 5 ml of isocyanate was added. After a further 48 hours, the reaction mixture was filtered and evaporated to an oil, The oil was triturated with heptane and the liqiud decanted off. The oil was dissolved in chloroform and chromatographed (HPLC) on a silica gel column, eluted with a linear gradient of chloroform to chloroform-methanol (19:1).

The desired fractions were combined and evaporated to an oil to afford 3.31 g of the title compound.

NMR: Consistent with the proposed structure.
MS: m/e=711 and some 212 (diphenylurea)
$C_{42}H_{37}N_3O_6S$.

Example 83

Preparation of [6-(N-phenylcarbamoyl)-2-[4-(N-phenylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone Hydrochloride.

3.2 g of [6-(N-phenylcarbamoyl)-2[4-(N-phenylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was disolved in ethyl acetate and filtered. Hydrogen chloride-ether was added to the solution and a white precipitate formed. The liquid was decanted off. The solid was dissolved in a small amount of acetone and filtered, then it is was evaporated to dryness to afford 270 mg of the title compound as a tan amorphous powder.

Elemental Analysis:	C	H	N
Calculated:	67.42	5.12	5.62
Found:	67.51	5.37	5.50

$C_{42}H_{38}ClN_3O_6S$.

By substantially following the procedures described above one skilled in the art can prepare the other compounds of Formula I.

β-Amyloid Production Inhibition Assay

Two cell lines [human kidney cell line 293 and Chines hamster ovary cell line (CHO)] were stably transfected

with the gene for amyloid precursor protein (APP-751) containing the double mutation Lys_{651}-Met_{652} to Asn_{651}-Leu_{652} (APP-751 numbering system) commonly called the Swedish mutation using the method described in Citron, et al., Nature (London), 360:672-674 (1992). The transfected cell lines wre designated as 293 751 SWE and CHO 751 SWE, and were plated in 96-well plates at an initial density of 2.5×10^4 and 1×10^4 cells per well, respectively, in Dulbecco's Minimal Essential Media (DMEM) supplemented with 10% fetal bovine serum.

Following overnight incubation at 37°C in an incubator equilibrated with 10% carbon dioxide, the media was removed and replaced with 200 µl per well of DMEM containing test compound at various concentration. Controls were also performed in which no test compound was added to the media in the wells. After a two hour pretreatment period, the media werew again removed and replaced with fresh media supplemented with the test compound and the cells were incubated for an additional two hours.

The test compound stocks were prepared in dimethylsulfoxide (DMSO) such that, at the highest conentration of tet compound, the concentration of DMSO in the wells never exceeded 0.5%.

After treatment, plates were centrifuged at 1200 rpm for about five minutes at room temperature to pellet cellular debris from the conditioned media. From each well, 100 µl of conditioned media were transferred into an enzyme-linked immunosorbent assay (ELISA) plate pre-coated with antibody 266, antibody specific for β-amyloid(13-28). D. Seubert, et al., Nature (London), 359:325-327 (1992). These ELISA plates were then stored at 4°C overnight. An ELISA assay employing labeled antibody 6C6, an antibody specific for β-amyloid(1-16), was run the next day to measure the amount of β-amyloid peptide produced.

The cytotoxic effects of the compounds of this invention were measured by a modification of the method of Hansen, et al., Journal of Immunological Methods, 119:203-210 (1989). To the cells remaining in the tissue culture plates

after the pelleting above was added 25 µl of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) stock solution (5 mg/ml) to a final concentration of 1 mg/ml. The cells were incubated at 37°C for about one hour at which time the cellular activity was stopped by the addition of an equal volume of MTT lysis buffer (20% w/v sodium dodecylfulfate in 50% N,N-dimethylformamide, pH 4.7). Complete extraction was achieved by overnight shaking at room temperature. The difference in the optical density at 562 nm (OD_{562}) and at 650 nm (OD_{650}) was measured in a spectrophotometer as an indicator of cellular viability.

The results of β-amyloid ELISA were fit to a standard curve and expressed as ng/ml of β-amyloid peptide. In order to normalize for cytotoxicity, the β-amyloid concentrations were divided by the MTT results and expressed as a percentage of the results from the drug-free controls.

Many of the compounds of Formula I were very active in the inhibition of β-amyloid production in the above assay while not causing significant cytotoxicity. The aggregation of β-amyloid peptide results in the activation of immune and inflammatory responses in affected areas of the brain. The β-amyloid peptide, upon assuming the conformation necessary for aggregation, also potentiates cytokine secretion, especially interleukin-6 and interleukin-8 release. The compounds of Formula I, in preventing the formation of β-amyloid aggregates, inhibit this cytokine release and, thereby, ameliorate the inflammatory component of Alzheimer's Disease.

The compounds of Formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The present invention also includes pharmaceutical compositions which contain, as the active ingredient, the compounds of Formula I associated with pharmaceutically acceptable carriers. In making the compositions of the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, cachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated

so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

For examples, dosages per day normally fall within the range of about 0.05 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

For prophylactic applications, the compounds of Formula I are administered to a host susceptible to Alzheimer's Disease or another physiological condition associated with an amyloidogenic peptide, but not necessarily already suffering from such disease. Such hosts may be identified by genetic screening and clinical analysis, as

described in the medical literature. See e.g., Goate, Nature, 349:704-706 (1991).

For preparing solid compositions such as tablets the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutiona, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable,

aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following examples illustrate the pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Capsules, each containing 15 mg of medicament, are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

Formulation Example 9

An intravenous formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	250.0 mg
Isotonic saline	1000 ml

Formulation Example 10

A topical formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Example 11

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

Ingredient	Quantity Per Tablet
Active Ingredient	10.0 mg
Glycerol	210.5 mg
Water	143.0 mg
Sodium Citrate	4.5 mg
Polyvinyl Alcohol	26.5 mg
Polyvinylpyrrolidone	15.5 mg
Total	410.0 mg

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

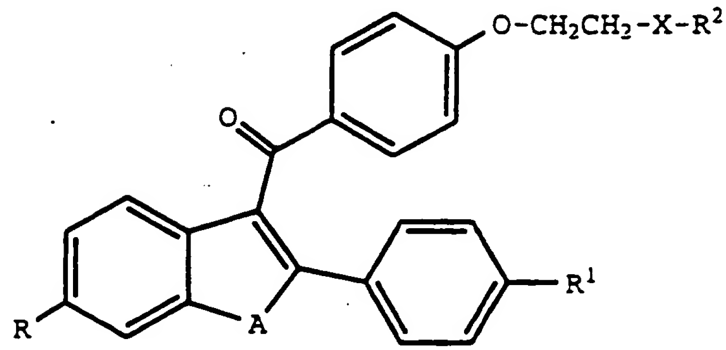
Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by refernce.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the

drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

Claims

1. The use of a compound of the formula



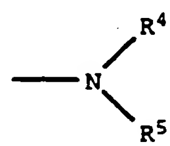
wherein:

A is -O-, $-S(O)_m-$, $-N(R^{11})-$, $-CH_2CH_2-$, or -CH=CH-;

m is 0, 1, or 2;

X is a bond or C_1-C_4 alkylidenyl;

R^2 is a group of the formula



wherein R^4 and R^5 are independently C_1-C_6 alkyl or combine to form, along with the nitrogen to which they are attached, a heterocyclic ring selected from the group consisting of hexamethyleneiminyl, piperazino, heptamethyleneiminyl, 4-methylpiperidinyl, imidazolinyl, piperidinyl, pyrrolidinyl, or morpholinyl;

R is hydroxy, halo, hydrogen, C_3-C_8 cycloalkyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkoxy, or phenyl, said phenyl being optionally substituted with one, two, or three moieties selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, chloro, fluoro, trifluoromethyl $-OSO_2-(C_1$-C_{10} alkyl) or $-O\overset{\displaystyle O}{\overset{\|}{C}}\underset{H}{N}-R^3$;

R^1 is hydroxy, halo, hydrogen, C_3-C_8 cycloalkyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkoxy, or phenyl, said phenyl being optionally substituted with one, two, or three moieties selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, chloro, fluoro, trifluoromethyl $-OSO_2-(C_1$-C_{10} alkyl) or $-O\overset{\displaystyle O}{\overset{\|}{C}}\underset{H}{N}-R^3$;

each R^3 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl where the substituent is halo, C_1-C_6 alkyl or C_1-C_6 alkoxy;

with the proviso that when X is a bond and A is -S-, R and R^1 are not both selected from the group consisting of hydroxy, methoxy, and C_2-C_7 alkanoyloxy;

or a pharmaceutically acceptable salt or solvate, in the preparation of a medicament useful for the treatment or prevention of a physiological disorder associated with an amyloidogenic peptide.

2. The use of a compound as claimed in Claim 1 wherein the compound is selected from the group consisting of 3-(4-methoxyphenyl)-4-[4-(2-pyrrolidin-1-ylethoxy)benzoyl-1,2-dihydronaphthalene, 3-phenyl-4-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-7-methoxy-1,2-dihydronaphthalene, 3-(4-methoxyphenyl)-4-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, 3-(4-hydroxyphenyl)-4-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, 3-(4-methoxyphenyl)-4-[4-[2-(hexamethyleneimin-1-yl)benzoyl]-1,2-dihydronaphthalene, 3-(4-methoxyphenyl)-4-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-1,2-dihydronaphthalene, 3-(4-methoxyphenyl)-4-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-7-methoxy-1,2-dihydronaphthalene, 3-(4-methoxyphenyl)-4-[4-[2-(N-methyl-1-pyrrolidinium)ethoxy]benzoyl]-1,2-dihydronaphthalene, 3-(4-methoxyphenyl)-4-[4-(2-dimethylaminoethoxy)benzoyl]-1,2-dihydronaphthalene, 3-(4-methoxyphenyl)-4-(4-diethylaminoethoxybenzoyl)-1,2-dihydronaphthalene, and 3-(4-methoxyphenyl)-4-(4-diisopropylaminoethoxybenzoyl)-1,2-dihydronaphthalene, or a pharmaceutically acceptable salt or solvate thereof.

3. The use of a compound as claimed in Claim 1 wherein the compound is selected from the group consisting of 2-(4-hydroxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran, 2-(4-hydroxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran, 2-(4-hydroxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]-6-hydroxybenzofuran, 2-(4-hydroxyphenyl)-3-[4-[2-(N,N-diethylamino)ethoxy]benzoyl]-6-hydroxybenzofuran, 2-(4-hydroxyphenyl)-3-[4-[2-(N,N-diisopropylamino)ethoxy]benzoyl]-6-hydroxybenzofuran, 2-(4-hydroxyphenyl)-3-[4-[2-(N,N-dimethylamino)ethoxy]benzoyl]-6-hydroxybenzofuran, 1-ethyl-2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-hydroxyindole, 2-(4-methoxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran, 2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxybenzofuran, 2-(4-methoxyphenyl)-3-[4-[2-(pyrrolidin-

1-yl)ethoxy]benzoyl]-6-methoxybenzofuran, 2-(4-methoxyphenyl)-3-[4-[2-(N,N-diethylamino)ethoxy]benzoyl]-6-methoxybenzofuran, 2-(4-methoxyphenyl)-3-[4-[2-(N,N-diisopropylamino)ethoxy]benzoyl]-6-methoxybenzofuran, 2-(4-methoxyphenyl)-3-[4-[2-(N,N-dimethylamino)ethoxy]benzoyl]-6-methoxybenzofuran, and 1-ethyl-2-(4-methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-6-methoxyindole, or a pharmaceutically acceptable salt or solvate.

4. The use of a compound as claimed in Claim 1 wherein the compound is selected from the group consisting of 2-(4-methoxyphenyl)-3-[4-[3-(hexamethyleneimin-1-yl)propoxy]benzoyl]benzo[b]thiophene, 2-(4-methoxyphenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-methoxyphenyl)-3-[4-[3-(piperidin-1-yl)propoxy]benzoyl]benzo[b]thiophene, 2-(4-methoxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-methoxyphenyl)-3-[4-[2-(N,N-diethylamino)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-methoxyphenyl)-3-[4-[2-(N,N-diisopropylamino)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-methoxyphenyl)-3-[4-[2-(N,N-dimethylamino)ethoxy]benzoyl]-benzo[b]thiophene, 2-(4-chlorophenyl)-3-[4-[2-(hexamethyleneimin-1-yl)ethoxy]benzoyl]-6-hydroxybenzo[b]thiophene, 2-(4-hydroxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-hydroxyphenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-hydroxyphenyl)-3-[4-[2-(N,N-diethylamino)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-hydroxyphenyl)-3-[4-[2-(N,N-diisopropylamino)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-hydroxyphenyl)-3-[4-[2-(N,N-dimethylamino)ethoxy]benzoyl]benzo[b]thiophene, 2-(4-chlorophenyl)-3-[4-[2-(pyrrolidin-1-yl)ethoxy]benzoyl]benzo[b]thiophene-1-oxide, and 2-(4-chlorophenyl)-3-[4-[2-(piperidin-1-

yl)ethoxy]benzoyl]benzo[b]thiophene-1-oxide, or a pharmaceutically acceptable salt.

5. The use of a compound as claimed in Claim 1 wherein the compound is selected from the group consisting of [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone, [6-(n-pentylsulfonoyl)-2-[4-(n-pentylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone, [6-(n-hexylsulfonoyl)-2-[4-(n-hexylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone, [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl][4-[3-(1-piperidinyl)propyloxy]phenyl]methanone, [6-(n-butylsulfonoyl)-2-[4-(n-butylsulfonoyl)phenyl]benzo[b]thien-3-yl]-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]methanone, [6-hydroxy-2-[4-(n-butylsulfonoyl)-phenyl]benzo[b]-thien-3-yl]-[4-[2-(1-piperidinyl)-ethoxy]phenyl]methanone, [6-n-butylsulfonyl-2-[4-hydroxyphenyl]benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, [6-[N-(4-chlorophenyl)carbamoyl]-2-[4-[N-(4-chlorophenyl)carbamoyl]phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, [6-(N-(n-butyl)carbamoyl]-2-[4-[N-(n-butyl)carbamoyl]phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, [6-(N-methylcarbamoyl)-2-[4-(N-methylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, [6-(N-ethylcarbamoyl)-2-[4-(N-ethylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, [6-(N-isopropylcarbamoyl)-2-[4-(N-iso-propylcarbamoyl)phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, and [6-(N-cyclohexylcarbamoyl)-2-[4-(N-cyclohexylcarbamoyl)phenyl]benzo[b]thienyl-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone, or a pharmaceutically acceptable salt or solvate thereof.

6. The use of a compound as claimed in Claim 1 wherein said physiological disorder associated with an amyloidogenic peptide is Alzheimer's Disease or Down Syndrome.

7. A pharmaceutical formulation comprising as an active ingredient a compound as claimed in any one of claims 1 to 5, associated with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

PCT/US94/14035

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/38; A61K 31/40; C07D 223/00, 403/00; C07F 9/06
US CL :514/410, 215, 256, 879; 540/581; 546/271; 548/117, 315.4, 364
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/410, 215, 256, 879; 540/581; 546/271; 548/117, 315.4, 364

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE, DERWENT
Search terms: benzofuran, benzothiophene, beta amyloid, mental diseas or disorder, Alzheimer or Down syndrome

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,847,254 (BOEGESOE ET AL) 11 JULY 1989, entire document.	1-7
Y	US, A, 4,946,863 (BOEGESOE ET AL) 07 AUGUST 1990, entire document.	1-7
Y	US, A, 5,185,350 (EFFLAND ET AL) 09 FEBRUARY 1993, entire document.	1-7
Y	US, A, 4,024,273 (BRENNER ET AL) 17 MAY 1977, see abstract.	1-5 and 7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 FEBRUARY 1995	14 MAR 1995
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